

Optimal Cutoff Levels of More Sensitive Cardiac Troponin Assays for the Early Diagnosis of Myocardial Infarction in Patients With Renal Dysfunction

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Background—It is unknown whether more sensitive cardiac troponin (cTn) assays maintain their clinical utility in patients with renal dysfunction. Moreover, their optimal cutoff levels in this vulnerable patient population have not previously been defined.

Methods and Results—In this multicenter study, we examined the clinical utility of 7 more sensitive cTn assays (3 sensitive and 4 high-sensitivity cTn assays) in patients presenting with symptoms suggestive of acute myocardial infarction. Among 2813 unselected patients, 447 (16%) had renal dysfunction (defined as Modification of Diet in Renal Disease–estimated glomerular filtration rate $<60 \text{ mL}\cdot\text{min}^{-1}\cdot 1.73 \text{ m}^{-2}$). The final diagnosis was centrally adjudicated by 2 independent cardiologists using all available information, including coronary angiography and serial levels of high-sensitivity cTnT. Acute myocardial infarction was the final diagnosis in 36% of all patients with renal dysfunction. Among patients with renal dysfunction and elevated baseline cTn levels (≥ 99 th percentile), acute myocardial infarction was the most common diagnosis for all assays (range, 45%–80%). In patients with renal dysfunction, diagnostic accuracy at presentation, quantified by the area under the receiver-operator characteristic curve, was 0.87 to 0.89 with no significant differences between the 7 more sensitive cTn assays and further increased to 0.91 to 0.95 at 3 hours. Overall, the area under the receiver-operator characteristic curve in patients with renal dysfunction was only slightly lower than in patients with normal renal function. The optimal receiver-operator characteristic curve–derived cTn cutoff levels in patients with renal dysfunction were significantly higher compared with those in patients with normal renal function (factor, 1.9–3.4).

Conclusions—More sensitive cTn assays maintain high diagnostic accuracy in patients with renal dysfunction. To ensure the best possible clinical use, assay-specific optimal cutoff levels, which are higher in patients with renal dysfunction, should be considered.

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Acute myocardial infarction (AMI) is a major cause of death and disability in Europe and the United States.¹ Its rapid and accurate diagnosis is critical for effective evidence-based medical management and treatment²⁻⁴ but is still an unmet clinical need. Delays in diagnosing disease

Editorial see p 2029
Clinical Perspective on p 2050

(“rule in”) hold back prompt use of evidence-based therapies.^{5,6} Delays in excluding AMI (“rule out”) interfere with

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evaluation of alternative diagnoses and contribute to medical errors and costs associated with crowding in the emergency department (ED).^{7–9}

For several reasons, patients with renal dysfunction merit particular attention. First, the incidence of AMI is increased in this vulnerable subgroup.^{10,11} Second, atypical clinical presentation of AMI may be more frequent.^{12,13} Third, left ventricular hypertrophy is common and often results in ECG changes that may mimic or obscure AMI. Fourth, patients with renal dysfunction are more prone to adverse events related to cardiovascular medication, for example, anticoagulation, as well as to cardiovascular procedures, including coronary angiography and coronary intervention.¹²

More sensitive cardiac troponin (cTn) assays with a limit of detection below the 99th percentile of a healthy reference population and improved precision have recently become available in clinical practice.^{14–16} While sensitive (s) assays allow the detection of cTn in 20% to 50% of healthy individuals, high-sensitivity (hs) assays allow the detection of cTn in even 50% to 90% of healthy individuals.¹⁷ These assays improved the early diagnosis of AMI in unselected patients with suspected AMI.^{18,19} However, their clinical utility in patients with renal dysfunction has recently been questioned.^{20–22} For example, elevated cTn levels above the 99th percentile were observed in up to 40% of patients with renal dysfunction and diagnoses other than AMI, potentially reducing the specificity for AMI.^{20–22} Although the 99th percentile is the undisputed reference value to diagnose AMI according to the universal definition of AMI, optimal clinical decision levels or cutoff levels at presentation to the ED may well differ from the 99th percentile.⁴

We therefore aimed to examine the diagnostic performance and to identify the optimal cutoff levels of 7 more sensitive cTn assays for the early diagnosis of AMI in patients with renal dysfunction.

Methods

Study Design and Population

The Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) is an ongoing prospective, international, multicenter study designed and coordinated by the University Hospital Basel (Basel, Switzerland).^{19,23,24} From April 2006 to June 2013, 3030 consecutive patients >18 years of age presenting to the ED with symptoms suggestive of AMI with an onset or peak within the last 12 hours were recruited after providing written informed consent. Although enrollment was completely independent of renal function, allowing the inclusion of a large number of patients with various degrees of renal dysfunction, patients with terminal kidney failure requiring regular long-term dialysis were excluded. For this analysis, patients were also excluded if no creatinine value at presentation to the ED was available ($n=18$), if none of the 7 investigational cTn assays were available at baseline ($n=107$), or if the final diagnosis remained unclear after adjudication ($n=92$; for details, see the online-only Data Supplement). Because some patients had missing data for some of the 7 investigational cTn assays, 7 assay-specific subcohorts with a large overlap but numerically not identical sizes were derived from the main cohort.

Renal function was quantified by estimating glomerular filtration rate (eGFR) with the use of the abbreviated Modification of Diet in Renal Disease Study equation based on plasma creatinine level, age, and sex, as described in detail elsewhere.^{25–27} For this analysis, renal dysfunction was defined as an eGFR of $<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$.²⁶ All creatinine measurements were performed on a Roche Modular PI analyzer with the enzymatic Creatinine-PAP method for quantification (Roche Diagnostics, Switzerland). Serum creatinine can be

converted from micromoles per liter to milligrams per deciliter by dividing by 88.4.

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. The authors designed the study, gathered and analyzed the data, vouch for the data and analysis, wrote the paper, and made the decision to submit it for publication. The assays were donated by the manufacturers, which had no role in the design of the study, the analysis of the data, the preparation of the manuscript, or the decision to submit for publication.

Routine Clinical Assessment

All patients underwent a clinical assessment that included medical history, physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood test, and chest radiography. Levels of cTn were measured at presentation and serially thereafter as long as clinically indicated. Timing and treatment of patients were left to discretion of the attending physician.

Adjudicated Final Diagnosis

Adjudication of the final diagnosis was performed centrally in a core laboratory (University Hospital Basel) and included levels of Roche hs-cTnT to take advantage of the higher sensitivity and higher overall diagnostic accuracy offered by hs-cTn assays (which allows the additional detection of small AMIs that were missed by the adjudication based on conventional cTn assays).^{20,21} Two independent cardiologists reviewed all available medical records—patient history, physical examination, results of laboratory testing (including hs-cTnT levels), radiological testing, ECG, echocardiography, cardiac exercise stress test, lesion severity, and morphology in coronary angiography—pertaining to the patient from the time of ED presentation to the 90-day follow up. Specifically, the patients' description of pain (typical, atypical, nonspecific), time since onset and peak of symptoms, and new ECG findings were taken into account for the adjudication of the final diagnosis. Furthermore, in patients with renal dysfunction, cTn levels of prior admissions were considered to assess whether the cTn levels were elevated previously. If the patient was taken to the catheterization laboratory, the presence of an acute occlusion, an acute culprit lesion with less than Thrombolysis in Myocardial Infarction grade 3 flow, and new wall motion abnormalities were considered evidence of AMI if observed in combination with an acute rise or fall in hs-cTnT. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist.

AMI was defined and cTn levels were interpreted as recommended in current guidelines.^{1,2,28} In brief, AMI was diagnosed when there was evidence of myocardial necrosis in association with a clinical setting consistent with myocardial ischemia. Myocardial necrosis was diagnosed by at least 1 cTn value above the 99th percentile of healthy individuals, together with a significant rise or fall.^{14,28,29} The criteria used to define rise or fall are described in detail in the Methods section in the online-only Data Supplement.

Investigational cTn Analysis

Details on the 7 cTn assays used in this analysis are given in the Methods section in the online-only Data Supplement. All 7 more sensitive cTn assays were centrally measured in a core laboratory. As for all cTn assays, the 7 more sensitive cTn assays are not biologically equivalent.

Follow-Up and Clinical End Points

After hospital discharge, patients were contacted after 3, 12, and 24 months by telephone calls or in written form. Information on death was furthermore obtained from the national registry on mortality, the diagnosis registry of the hospitals, and the family physicians' records. The primary prognostic end point was survival within 2 years.

Statistical Analysis

Details on statistical analysis can be found in the online-only Data Supplement.

Results

Patient Characteristics

Among the 2813 unselected patients in the total cohort, 447 (16%) had renal dysfunction (Table 1). Among the

7 assay-specific subcohorts, baseline characteristics and final diagnoses were comparable (Table I in the online-only Data Supplement). Patients with renal dysfunction differed from patients with normal renal function in multiple baseline characteristics, including higher prevalence

Table 1. Baseline Patient Characteristics

	All Patients (n=2813)	Normal Renal Function (n=2366)	Renal Dysfunction* (n=447)	P Value†	Patients With Renal Dysfunction		
					AMI		P Value‡
					Yes (n=160)	No (n=287)	
Male sex, n (%)	1907 (68)	1656 (70)	251 (56)	<0.001	95 (59)	156 (54)	0.305
Age, median (Q1, Q3), y	62 (49, 74)	58 (48, 70)	77 (70, 83)	<0.001	79 (73, 85)	77 (70, 82)	0.004
Cardiovascular risk factors, n (%)							
Diabetes mellitus	488 (17)	363 (15)	125 (28)	<0.001	49 (31)	76 (26)	0.039
Current smoking	720 (26)	675 (29)	45 (10)	<0.001	22 (14)	23 (8)	0.083
History of smoking	1013 (36)	823 (35)	190 (43)	<0.001	58 (37)	132 (46)	0.089
Hypercholesterolemia	1407 (50)	1099 (46)	308 (69)	<0.001	119 (74)	189 (66)	0.062
Hypertension	1741 (62)	1342 (57)	399 (89)	<0.001	148 (93)	251 (88)	0.099
History, n (%)							
Known coronary artery disease	965 (34)	714 (30)	251 (56)	<0.001	96 (60)	155 (54)	0.221
Previous myocardial infarction	653 (23)	475 (20)	178 (40)	<0.001	70 (44)	108 (38)	0.205
Previous revascularization	768 (27)	590 (25)	178 (40)	<0.001	65 (41)	113 (39)	0.795
Peripheral artery disease	171 (6)	112 (5)	59 (13)	<0.001	27 (17)	32 (11)	0.086
Previous stroke	154 (6)	106 (5)	48 (11)	<0.001	22 (14)	26 (9)	0.125
Vital status, median (Q1, Q3)							
Heart rate, bpm	76 (66, 89)	76 (66, 89)	74 (63, 91)	0.162	79 (63, 96)	73 (63, 88)	0.033
Systolic blood pressure, mm Hg	141 (127, 159)	142 (128, 159)	138 (120, 157)	0.001	137 (119, 159)	139 (120, 159)	0.213
Diastolic blood pressure, mm Hg	82 (72, 92)	83 (74, 92)	75 (65, 86)	<0.001	74 (65, 84)	76 (65, 87)	0.157
Body mass index, kg/m ²	26 (24, 30)	26 (24, 30)	27 (24, 30)	0.414	25 (23, 28)	27 (25, 31)	<0.001
ECG, n (%)							
ST-segment elevation	134 (5)	110 (5)	24 (6)	0.010	23 (15)	1 (0.4)	<0.001
ST-segment depression	322 (11)	228 (10)	94 (21)	<0.001	61 (38)	33 (11)	<0.001
T-wave inversion	375 (13)	287 (12)	88 (20)	<0.001	46 (29)	42 (15)	<0.001
Left bundle-branch block	81 (3)	52 (2)	29 (7)	<0.001	16 (10)	13 (5)	0.024
Diagnostic examinations and interventions,‡ n (%)							
Stress testing	711 (25)	626 (27)	85 (19)	0.001	20 (13)	65 (23)	0.009
Coronary angiographies	739 (26)	590 (25)	149 (33)	<0.001	94 (59)	55 (19)	<0.001
Coronary interventions	443 (16)	357 (15)	86 (19)	0.027	64 (40)	22 (8)	<0.001
CABG	64 (2)	52 (2)	12 (3)	0.527	10 (6)	2 (1)	<0.001
Renal function, median (Q1, Q3)							
Creatinine, $\mu\text{mol/L}$	76 (65, 90)	72 (63, 83)	116 (99, 139)	<0.001	120 (106, 147)	115 (96, 135)	0.038
MDRD eGFR, $\text{mL}\cdot\text{min}^{-1}\cdot 1.73\text{ m}^{-2}$	85 (69, 101)	90 (77, 104)	49 (39, 55)	<0.001	47 (37, 55)	49 (41, 55)	0.089
Stages of renal dysfunction, n (%)							
eGFR 30–59 $\text{mL}\cdot\text{min}^{-1}\cdot 1.73\text{ m}^{-2}$	403 (14)	...	403 (90)		141 (88)	262 (91)	0.491
eGFR 15–29 $\text{mL}\cdot\text{min}^{-1}\cdot 1.73\text{ m}^{-2}$	34 (1)	...	34 (8)	NA	14 (9)	20 (7)	
eGFR <15 $\text{mL}\cdot\text{min}^{-1}\cdot 1.73\text{ m}^{-2}$	10 (0.4)	...	10 (2)		5 (3)	5 (2)	

AMI indicates acute myocardial infarction; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; Q1, quartile 1; and Q3, quartile 3.

*Renal dysfunction was diagnosed if the MDRD eGFR was $<60\text{ mL}\cdot\text{min}^{-1}\cdot 1.73\text{ m}^{-2}$ at presentation.

†The χ^2 test was used for comparison of proportions.

‡Performed during or directly after the index visit (within 1 month).

of cardiovascular risk factors, previous myocardial infarction, stroke, and ECG abnormalities. In patients with renal dysfunction, the total rate of additional cardiac testing related to AMI diagnosis (in addition to detailed history, ECG, cTn, chest x-ray), including coronary angiography or cardiac stress testing with or without imaging, was similar to that of patients with normal renal function (52% in both groups; $P=NS$). Coronary angiography was performed more frequently in patients with renal dysfunction (33%) compared with patients with normal renal function (25%; $P<0.001$).

AMI was the adjudicated final diagnosis in 36% of patients with renal dysfunction compared with 18% in patients with normal renal function ($P<0.001$). Both type I AMI and type II AMI were more frequent in patients with renal dysfunction. Among patients with non-ST-segment-elevation myocardial infarction, type II AMI was seen in 23% of patients with renal dysfunction compared with 10% in patients with normal renal function ($P<0.001$; Table II in the online-only Data Supplement). Disagreement between the 2 independent cardiologists adjudicating the final diagnosis was more common in patients with renal dysfunction compared with patients with normal renal function (8.7% versus 5.9%; $P=0.023$) and tended to be more common in patients presenting with elevated levels of hs-cTnT compared with patients presenting with normal levels of hs-cTnT (7.4% versus 5.7%; $P=0.063$).

cTn Levels at Presentation

In patients with renal dysfunction and in patients with normal renal function, cTn levels at presentation, as assessed by all 7 more sensitive cTn assays, were significantly higher in patients whose final diagnosis was AMI compared with those with other diagnoses ($P<0.001$ for comparisons). Among the patients whose final diagnosis was not AMI, patients with renal dysfunction had significantly higher baseline levels of all 7 more sensitive cTn assays compared

with patients with normal renal function ($P<0.001$ for all comparisons with patients with normal renal function). Overall, 12% of patients with renal dysfunction and a final diagnosis other than AMI had elevated baseline levels above the 99th percentile with Abbott-Architect s-cTnI, 20% with Siemens-Ultra s-cTnI, 12% with Beckman-Coulter Accu s-cTnI, 71% with Roche hs-cTnT, 17% with Abbott hs-cTnI, 46% with Siemens hs-cTnI, and 54% with Beckman-Coulter hs-cTnI. Among patients with normal renal function, the percentages were significantly lower (7%, 7%, 7%, 15%, 6%, 23%, and 21%, respectively; $P<0.001$ for all comparisons; Figure 1). Among patients with renal dysfunction and elevated (≥ 99 th percentile) baseline cTn levels, AMI was the most common diagnosis for all assays (range, 45%–80%; Figure 2). Among patients with renal dysfunction and normal baseline cTn levels, noncardiac cause of chest pain is the most common diagnosis (Figure I in the online-only Data Supplement). Details on median absolute changes of hs-cTnT during serial sampling are shown in Table IIIA and IIIB in the online-only Data Supplement.

Correlations Between cTn levels and eGFR

Among patients with final diagnoses other than AMI, all 7 more sensitive cTn assays correlated significantly and inversely with renal function as quantified with the Modification of Diet in Renal Disease eGFR formula (correlation coefficient, r , ranging from -0.448 to -0.222 ; $P<0.001$ for all correlations). The correlation between eGFR and hs-cTnT was stronger compared with the correlation between eGFR and hs-cTnI as measured with all assays (Figure II in the online-only Data Supplement).

Diagnostic Accuracy of More Sensitive cTn

In patients with renal dysfunction, the diagnostic accuracy for measurements obtained at presentation, as quantified by the area under the receiver-operating characteristic curve (AUC), overall was high (AUC, 0.87–0.89) for all 7 more

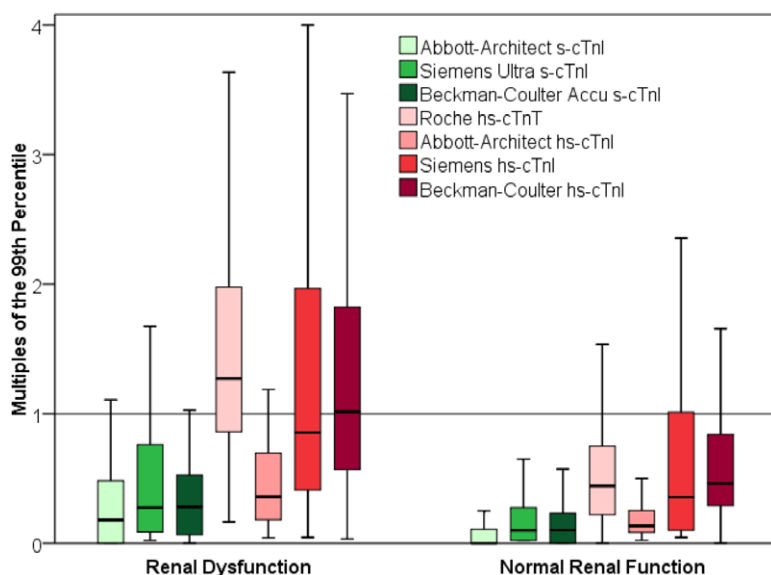


Figure 1. Baseline levels of more sensitive cardiac troponin (cTn) assays at presentation in patients with final diagnosis other than acute myocardial infarction. cTn levels are displayed as multiples of the 99th percentile. Boxes represent interquartile ranges; whiskers display ranges (without outliers further than 1.5 interquartile ranges). **Left,** In patients with renal dysfunction. **Right,** In patients with normal renal function. hs indicates high-sensitivity; and s, sensitive.

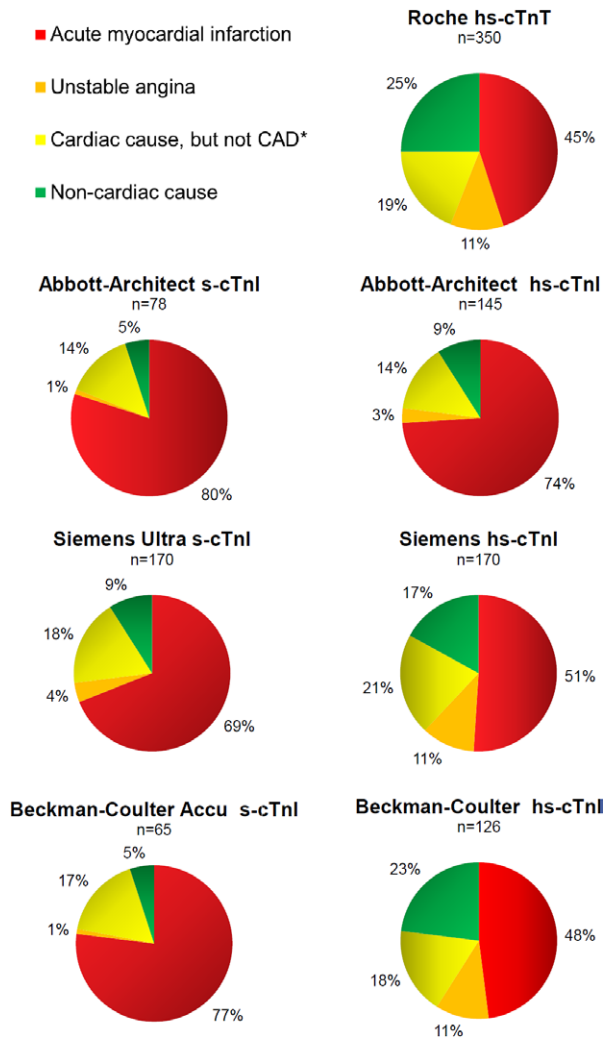


Figure 2. Distribution of final diagnoses in patients with renal dysfunction and cardiac troponin (cTn) levels above the 99th percentile at presentation. hs Indicates high-sensitivity; and s, sensitive. *Coronary artery disease.

sensitive-cTn assays (Table 2 and Figure 3). Diagnostic accuracy further increased to 0.91 to 0.95 for samples obtained at 3 hours (Table IV in the online-only Data Supplement) and for combinations of the baseline level with early absolute changes (eg, at 1 hour: AUC, 0.90–0.93; Table V in the online-only Data Supplement). No significant differences among the 7 more sensitive cTn assays were observed ($P=NS$ for all comparisons). Overall, the AUCs in patients with renal dysfunction were only slightly lower than in patients with normal renal function. The AUC for levels obtained at presentation in patients with normal renal function was 0.91 to 0.94 ($P<0.05$ for the 4 assays with the largest sample size/comparisons with patients with renal dysfunction).

Among patients with different stages of renal dysfunction, AUCs for all more sensitive cTn assays were lower in the lowest tertile of renal function ($eGFR \leq 42$ mL·min⁻¹·1.73 m⁻²) compared with the intermediate tertile ($eGFR$, 42–53 mL·min⁻¹·1.73 m⁻²). This difference was statistically significant for the 3 assays with the largest sample

size. In contrast, the AUCs were comparable for all assays in patients in the highest tertile ($eGFR >53$ mL·min⁻¹·1.73 m⁻²) and the intermediate tertile (Table VI in the online-only Data Supplement).

Diagnostic Performance in the Early Diagnosis of AMI at the 99th Percentile

Overall, at the 99th percentile, all 7 more sensitive cTn assays showed higher sensitivity (77%–98%) in patients with renal dysfunction compared with patients with normal renal function. This increase in sensitivity, however, was associated with a decrease in specificity (32%–89%; $P<0.001$; Table VIIA and VIIB in the online-only Data Supplement). Sensitivity and specificity at the 99th percentile differed markedly between the more sensitive cTn assays. For 3 of the 4 hs-cTn assays, the specificity and positive predictive value at the 99th percentile were <60% and 55%, respectively.

Optimal Cutoff Levels for cTn in the Early Diagnosis of AMI

The optimal cutoff levels to separate AMI from other conditions underlying acute chest pain in the ED determined by the receiver-operator characteristic curve analysis in patients with renal dysfunction were close to the 99th percentile for the 3 s-cTn assays (1.0 times the 99th percentile for Abbott-Architect s-cTnI, 1.2 times the 99th percentile for Siemens Ultra s-cTnI, and 0.9 times the 99th percentile for Beckman-Coulter Accu s-cTnI) and substantially higher for most hs-cTn assays (2.1 times the 99th percentile for Roche hs-cTnT, 1.1 times the 99th percentile for Abbott-Architect hs-cTnI, 3.6 times the 99th percentile for Siemens hs-cTnI, and 2.8 times the 99th percentile for Beckman-Coulter hs-cTnI).

Overall, all cutoff levels fulfilling a predefined criteria (derived by receiver-operator characteristic curve, optimized for sensitivity, optimized for specificity) were higher in patients with renal dysfunction compared with patients with normal renal function. The optimal receiver-operator characteristic curve–derived cutoff levels in patients with renal dysfunction were 1.9 to 3.4 times the levels in patients with normal renal function.

Prognostic Performance of More Sensitive cTn in Renal Dysfunction

Median follow-up was 759 days (first quartile, 455 days; third quartile, 895 days). Overall, 182 patients (6%) died during follow-up. Cumulative survival at 2 years was 79% in patients with renal dysfunction versus 96% in patients with normal renal function (log-rank $P<0.001$; Figure III in the online-only Data Supplement). Survival was 67% among patients with renal dysfunction and AMI versus 85% in patients with renal dysfunction and diagnoses other than AMI (log-rank $P<0.001$). Levels of cTn as measured with all 7 more sensitive cTn assays were higher in deceased patients compared with survivors and accordingly predicted long-term survival (Table VIII and Figure IV in the online-only Data Supplement).

Table 2. Diagnostic Performance of cTn at Presentation in Patients With Renal Dysfunction and in Patients With Normal Renal Function

	Normal Renal Function		Renal Dysfunction		
Assay	n	ROC AUC (95% CI)	n	ROC AUC (95% CI)	P Value*
s-cTn assays					
Abbott-Architect s-cTnI	1095	0.91 (0.89–0.94)	219	0.89 (0.85–0.94)	0.449
Siemens Ultra s-cTnI	2247	0.92 (0.91–0.94)	416	0.87 (0.84–0.91)	0.013
Beckman-Coulter Accu s-cTnI	964	0.92 (0.89–0.94)	190	0.89 (0.84–0.94)	0.576
hs-cTn assays					
Roche hs-cTnT	2366	0.94 (0.93–0.95)	447	0.87 (0.84–0.91)	<0.001
Abbott-Architect hs-cTnI	1921	0.94 (0.93–0.95)	366	0.87 (0.83–0.91)	<0.001
Siemens hs-cTnI	1591	0.94 (0.92–0.95)	283	0.89 (0.84–0.93)	0.034
Beckman-Coulter hs-cTnI	964	0.93 (0.90–0.95)	190	0.89 (0.84–0.94)	0.217

CI indicates confidence interval; cTn, cardiac troponin; hs, high-sensitivity; ROC AUC, area under the receiver-operating characteristic curve; and s, sensitive.

*Comparisons of the ROC AUC of patients with renal dysfunction and normal renal function.

Discussion

In this multicenter study, we examined the diagnostic performance and identified the optimal cutoff levels of 7 more sensitive cTn assays for the early diagnosis of AMI in patients with renal dysfunction. We report 7 novel findings that have important clinical implications for the early diagnosis of AMI in that they clearly highlight that more sensitive cTn assays maintain high diagnostic utility in patients with renal dysfunction as long as optimized cutoff levels are used.

First, cTn levels at presentation, as assessed by all 7 more sensitive cTn assays, were significantly higher in patients whose final diagnosis was AMI compared with those with other final diagnoses. The prevalence of elevated cTn levels above the 99th percentile in patients with renal dysfunction and a final diagnosis other than AMI differed substantially among the 7 more sensitive cTn assays, ranging from 12% to 71%. Second, despite this, AMI remained the most common final diagnosis among patients with elevated cTn levels for all assays (range, 45%–80%). Third and perhaps most important, for all 7 more sensitive cTn assays, the diagnostic accuracy at presentation was high in patients with renal dysfunction with an AUC ranging from 0.87 to 0.89 and further increased for later sampling points and for combinations of the baseline level with early absolute changes. The diagnostic accuracy of the more sensitive cTn assays at presentation was only slightly lower compared with that in patients with normal renal function. Fourth, diagnostic accuracies were comparable among the 7 more sensitive cTn assays in patients with renal dysfunction with no systematic superiority of hs-cTn assays over sensitive assays. Fifth, at the 99th percentile, all cTn assays showed higher sensitivity but lower specificity in patients with renal dysfunction compared with patients with normal renal function, reflecting the higher baseline levels observed in patients with renal dysfunction even in the absence of AMI. Sixth, the receiver-operator characteristic curve–derived optimal cutoff levels

in patients with renal dysfunction were 2- to 3-times higher in patients with renal dysfunction compared with patients with normal renal function. Seventh, cTn as measured with all 7 more sensitive cTn assays also retained prognostic value and predicted 2-year survival in patients with renal dysfunction. These findings extend the observations made in previous studies investigating the prognostic value of cTn in various other settings.^{30–33}

Although the 99th percentile of healthy individuals is the undisputed reference value to diagnose AMI according to the universal definition of AMI,⁴ optimal clinical decision levels or cutoff levels at presentation to the ED may well differ from the 99th percentile of healthy individuals. For example, if we aim to rule out AMI at presentation to the ED, the cutoff level achieving high sensitivity and negative predictive value will likely be lower than the 99th percentile to allow for a further increase in cTn during serial sampling. Alternatively, if we aim to rule in AMI at presentation to the ED, the cutoff level achieving high specificity and positive predictive value will likely be higher than the 99th percentile because mild elevations in cTn can often be caused by conditions other than AMI. The fine-tuning of clinical decision levels for specific clinical settings (eg, ED) and patient populations (eg, renal dysfunction) is a key step in the clinical implementation of novel diagnostic tools such as biomarkers and has recently been done successfully for other biomarkers such as B-type natriuretic peptide and procalcitonin.^{34–36}

Our findings highlight that these clinical decision levels are assay specific and need to be determined for each assay individually. For example, the clinical decision level for cTn assay A achieving a specificity of 90% in patients with renal dysfunction cannot be reliably extrapolated from observations made with cTn assay B. To some extent, this requirement is explained by biochemical differences among the cTn assays and the challenges to define a healthy reference population to determine the 99th percentile.^{4,14} The 99th percentile is currently derived for each assay individually in

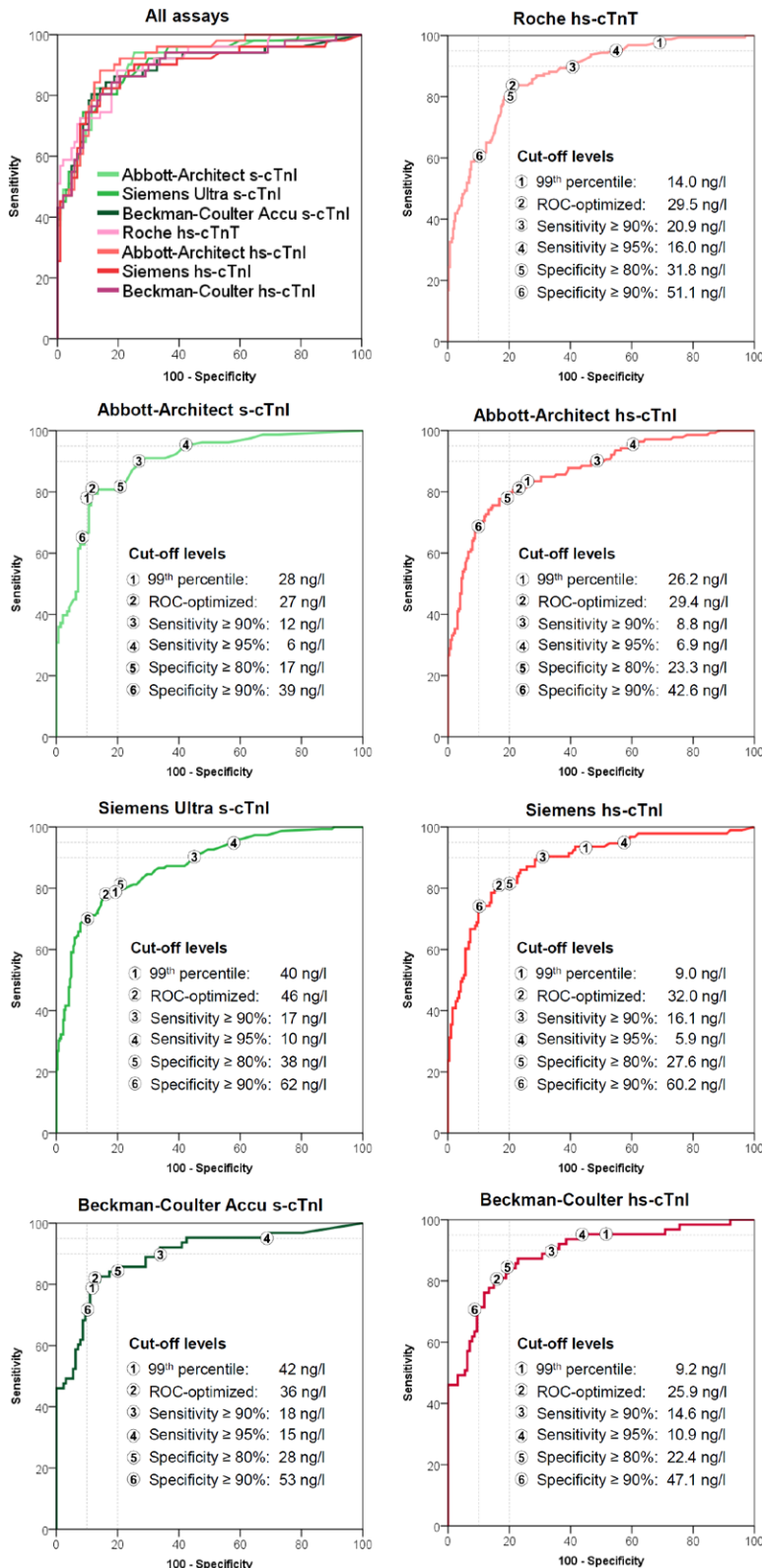


Figure 3. Diagnostic performance of cardiac troponin (cTn) at presentation in renal dysfunction. Receiver-operating characteristic (ROC) curves are describing the diagnostic performance of the 3 sensitive (s; green) and 4 high-sensitivity (hs; red) cTn assays at presentation for the diagnosis of acute myocardial infarction in patients with renal dysfunction. The figure containing multiple curves (upper left corner) is based on the subset of patients in whom data for all 7 assays are available. The figures for the individual assays are based on all patients with available data for the respective assays to maximize precision for the determination of the respective predefined cutoff levels, which are marked as follows: 1=99th percentile, 2=optimal cutoff derived from the ROC curve, 3=sensitivity ≥90%, 4=sensitivity ≥95%, 5=sensitivity ≥80%, and 6=sensitivity ≥90%.

unstandardized, healthy cohorts that differ from community-based cohorts.³⁷ In addition, as shown, for example, by Gore et al,³⁷ the 99th percentile of community-based cohorts also differs largely and will depend on the cohort's mean age and the prevalence of cardiovascular comorbidities and renal

dysfunction. Some of the differences observed for the performance of the more sensitive cTn assays at the respective 99th percentile of healthy individuals may be associated at least in part with differences between the cohorts of healthy individuals chosen for the determination of the 99th percentile.

Of note, the 99th percentile of the Roche hs-cTnT, the assay used for the adjudication of the final diagnosis in the present analysis, has rather consistently been reported to be ≈ 14 ng/L, whereas the findings for other hs-cTn assays have been more variable.³⁸

Our data also confirm previous observations that the diagnostic challenge in patients with renal dysfunction appears to be largely confined to patients presenting without persistent ST-segment elevation and that ST-segment depression or T-wave inversion is much more common in patients with renal dysfunction, even in the absence of AMI.²⁻⁴

This study is the first analysis that specifically examined diagnostic performance of more sensitive cTn assays in patients presenting to the ED with renal dysfunction and symptoms suggestive of AMI. Our findings may also help to better put into perspective a contradictory conclusion derived from a recent retrospective single-center study analyzing all ED patients with renal dysfunction regardless of symptoms, clinical gestalt, and clinical pretest probability for AMI, which reported lower-than-expected diagnostic accuracy of hs-cTnT for AMI.²² In that cohort, only 37% of patients had a clinical suspicion of AMI, and trauma, stroke, epileptic seizures, and acute heart failure accounted for the majority of patients. In those patients, the clinical role of measuring cTn is controversial and not at all comparable to the measurement in patients presenting with suspected AMI. In addition, that population of patients provides important methodological challenges for the adjudication of AMI based on the information obtained during routine clinical care, which might have further contributed to those findings. The findings from this prospective multicenter study using a gold standard diagnosis centrally adjudicated by 2 independent cardiologists should help to avoid possible misunderstandings related to the diagnostic utility of more sensitive cTn assays in patients with suspected AMI and renal dysfunctions.

The following limitations of the present study merit consideration. First, we evaluated 7 more sensitive-cTn assays. We hypothesize that our findings can be generalized to other cTn assays with similar sensitivity and precision. However, additional studies need to confirm this hypothesis. Second, in this ongoing prospective study, the subgroup analysis of patients with renal dysfunction was not predefined at the time of the writing of the first protocol but was added as an amendment in 2009, when we were still blinded to the results. Third, we cannot comment on the clinical utility of more sensitive cTn assays in patients undergoing dialysis because such patients were excluded from our study.³⁹ Fourth, to reflect the clinical information available to the ED physician when interpreting cTn levels, we classified renal dysfunction according to eGFR on the basis of the serum creatinine level obtained in the ED. Accordingly, this classification differs from the definition of chronic kidney disease, which would require renal dysfunction to be present for 3 months.²⁵⁻²⁷

Conclusions

More sensitive cTn assays maintain high diagnostic accuracy in patients with suspected AMI and renal dysfunction. To ensure the best possible clinical use, assay-specific optimal

cutoff levels, which are higher in patients with renal dysfunction, should be considered.

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Disclosures

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References

1. Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE Jr, Ettinger SM, Fesmire FM, Ganiats TG, Lincoff AM, Peterson ED, Philippides GJ, Theroux P, Wenger NK, Zidar JP, Anderson JL; 2012 Writing Committee Members; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2012;126:875-910. doi: 10.1161/CIR.0b013e318256f1e0.
2. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D; ESC Committee for Practice Guidelines. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:2999-3054. doi: 10.1093/eurheartj/ehr236.
3. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso JE, Tracy CM, Woo YJ, Zhao DX; Force CAT. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127:529-555.
4. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller GA, Bonow R, Van der Wall EE, Bassand JP, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox KA, Hamm CW, Ohman EM, Simoons ML, Poole-Wilson PA, Gurfinkel EP, Lopez-Sendon JL, Pais P, Mendis S, Zhu JR, Wallentin LC, Fernández-Avilés F, Fox KM, Parkhomenko AN, Priori SG, Tendera M, Voipio-Pulkki LM, Vahanian A, Camm AJ, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Morais J, Brener S, Harrington R, Morrow D, Lim M, Martinez-Rios MA, Steinhilb S, Levine GN, Gibler WB, Goff D, Tubaro M, Dudek D, Al-Attar N; Joint ESC/ACCF/AHA/WHF Task Force for the

- Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Circulation*. 2007;116:2634–2653. doi: 10.1161/CIRCULATIONAHA.107.187397.
5. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, Chavey WE 2nd, Fesmire FM, Hochman JS, Levin TN, Lincoff AM, Peterson ED, Theroux P, Wenger NK, Wright RS, Smith SC Jr; 2011 Writing Group Members; ACCF/AHA Task Force Members. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;123:e426–e579. doi: 10.1161/CIR.0b013e318212bb8b.
6. Deleted in proof.
7. Forberg JL, Henriksen LS, Edenbrandt L, Ekelund U. Direct hospital costs of chest pain patients attending the emergency department: a retrospective study. *BMC Emerg Med*. 2006;6:6. doi: 10.1186/1471-227X-6-6.
8. Tiemann O. Variations in hospitalisation costs for acute myocardial infarction: a comparison across Europe. *Health Econ*. 2008;17(suppl):S33–S45. doi: 10.1002/hec.1322.
9. Pines JM, Pollack CV Jr, Diercks DB, Chang AM, Shofer FS, Hollander JE. The association between emergency department crowding and adverse cardiovascular outcomes in patients with chest pain. *Acad Emerg Med*. 2009;16:617–625. doi: 10.1111/j.1553-2712.2009.00456.x.
10. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305. doi: 10.1056/NEJMoa041031.
11. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004;351:1285–1295. doi: 10.1056/NEJMoa041365.
12. Aronow WS, Ahn C, Mercado AD, Epstein S. Prevalence of coronary artery disease, complex ventricular arrhythmias, and silent myocardial ischemia and incidence of new coronary events in older persons with chronic renal insufficiency and with normal renal function. *Am J Cardiol*. 2000;86:1142–1143, A9.
13. Nakamura S, Uzu T, Inenaga T, Kimura G. Prediction of coronary artery disease and cardiac events using electrocardiographic changes during hemodialysis. *Am J Kidney Dis*. 2000;36:592–599. doi: 10.1053/ajkd.2000.16198.
14. Apple FS, Jesse RL, Newby LK, Wu AH, Christenson RH; National Academy of Clinical Biochemistry; IFCC Committee for Standardization of Markers of Cardiac Damage. National Academy of Clinical Biochemistry and IFCC Committee for Standardization of Markers of Cardiac Damage laboratory medicine practice guidelines: analytical issues for biochemical markers of acute coronary syndromes. *Circulation*. 2007;115:e352–e355. doi: 10.1161/CIRCULATIONAHA.107.182881.
15. Apple FS, Smith SW, Pearce LA, Ler R, Murakami MM. Use of the Centaur Tni-Ultra assay for detection of myocardial infarction and adverse events in patients presenting with symptoms suggestive of acute coronary syndrome. *Clin Chem*. 2008;54:723–728. doi: 10.1373/clinchem.2007.097162.
16. Melanson SE, Morrow DA, Jarolim P. Earlier detection of myocardial injury in a preliminary evaluation using a new troponin I assay with improved sensitivity. *Am J Clin Pathol*. 2007;128:282–286. doi: 10.1309/Q9W5HJTT24GQCXXX.
17. Apple FS. A new season for cardiac troponin assays: it's time to keep a scorecard. *Clin Chem*. 2009;55:1303–1306. doi: 10.1373/clinchem.2009.128363.
18. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, Bickel C, Baldus S, Warnholtz A, Fröhlich M, Sinning CR, Eleftheriadis MS, Wild PS, Schnabel RB, Lubos E, Jachmann N, Genth-Zotz S, Post F, Nicaud V, Tiret L, Lackner KJ, Münzel TF, Blankenberg S. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. *N Engl J Med*. 2009;361:868–877. doi: 10.1056/NEJMoa0903515.
19. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, Biedert S, Schaub N, Buerge C, Potocki M, Noveanu M, Breidthardt T, Twerenbold R, Winkler K, Bingisser R, Mueller C. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med*. 2009;361:858–867. doi: 10.1056/NEJMoa0900428.
20. Flores-Solís LM, Hernández-Domínguez JL. Cardiac troponin I in patients with chronic kidney disease stage 3 to 5 in conditions other than acute coronary syndrome. *Clin Lab*. 2014;60:281–290.
21. Chen S, Huang C, Wu B, Lian X, Mei X, Wan J. Cardiac troponin I in non-acute coronary syndrome patients with chronic kidney disease. *PLoS One*. 2013;8:e82752. doi: 10.1371/journal.pone.0082752.
22. Pfortmueller CA, Funk GC, Marti G, Leichter AB, Fiedler GM, Schwarz C, Exadaktylos AK, Lindner G. Diagnostic performance of high-sensitive troponin T in patients with renal insufficiency. *Am J Cardiol*. 2013;112:1968–1972. doi: 10.1016/j.amjcard.2013.08.028.
23. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, Bassetti S, Steuer S, Winkler K, Peter F, Meissner J, Haaf P, Potocki M, Drexler B, Osswald S, Mueller C. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. *Circulation*. 2011;124:136–145. doi: 10.1161/CIRCULATIONAHA.111.023937.
24. Reiter M, Twerenbold R, Reichlin T, Haaf P, Peter F, Meissner J, Hochholzer W, Stelzig C, Freese M, Heinisch C, Breidthardt T, Freidank H, Winkler K, Campodarve I, Gea J, Mueller C. Early diagnosis of acute myocardial infarction in the elderly using more sensitive cardiac troponin assays. *Eur Heart J*. 2011;32:1379–1389. doi: 10.1093/eurheartj/ehr033.
25. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation: Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461–470.
26. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med*. 2003;139:137–147.
27. Levey AS. Clinical practice: nondiabetic kidney disease. *N Engl J Med*. 2002;347:1505–1511. doi: 10.1056/NEJMcp013462.
28. Thygesen K, Alpert JS, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Eur Heart J*. 2007;28:2525–2538. doi: 10.1093/eurheartj/ehm355.
29. Apple FS, Wu AH, Jaffe AS. European Society of Cardiology and American College of Cardiology guidelines for redefinition of myocardial infarction: how to use existing assays clinically and for clinical trials. *Am Heart J*. 2002;144:981–986. doi: 10.1067/mhj.2002.124048.
30. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, Tjora S, Domanski MJ, Gersh BJ, Rouleau JL, Pfeffer MA, Braunwald E; Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial Investigators. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med*. 2009;361:2538–2547. doi: 10.1056/NEJMoa0805299.
31. Eggers KM, Lagerqvist B, Venge P, Wallentin L, Lindahl B. Persistent cardiac troponin I elevation in stabilized patients after an episode of acute coronary syndrome predicts long-term mortality. *Circulation*. 2007;116:1907–1914. doi: 10.1161/CIRCULATIONAHA.107.708529.
32. Michos ED, Wilson LM, Yeh HC, Berger Z, Suarez-Cuervo C, Stacy SR, Bass EB. Prognostic value of cardiac troponin in patients with chronic kidney disease without suspected acute coronary syndrome: a systematic review and meta-analysis. *Ann Intern Med*. 2014;161:491–501. doi: 10.7326/M14-0743.
33. Stacy SR, Suarez-Cuervo C, Berger Z, Wilson LM, Yeh HC, Bass EB, Michos ED. Role of troponin in patients with chronic kidney disease and suspected acute coronary syndrome: a systematic review. *Ann Intern Med*. 2014;161:502–512. doi: 10.7326/M14-0746.
34. Maisel AS, Clopton P, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Steg G, Westheim A, Knudsen CW, Perez A, Kazanegra R, Bhalla V, Herrmann HC, Aumont MC, McCullough PA; BNP Multinational Study Investigators. Impact of age, race, and sex on the ability of B-type natriuretic peptide to aid in the emergency diagnosis of heart failure: results from the Breathing Not Properly (BNP) multinational study. *Am Heart J*. 2004;147:1078–1084. doi: 10.1016/j.ahj.2004.01.013.
35. Mueller C, Scholer A, Laule-Kilian K, Martina B, Schindler C, Buser P, Pfisterer M, Perruchoud AP. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med*. 2004;350:647–654. doi: 10.1056/NEJMoa031681.
36. Christ-Crain M, Stolz D, Bingisser R, Müller C, Miedinger D, Huber PR, Zimmerli W, Harbarth S, Tamm M, Müller B. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a

- randomized trial. *Am J Respir Crit Care Med*. 2006;174:84–93. doi: 10.1164/rccm.200512-1922OC.
37. Gore MO, Seliger SL, Defilippi CR, Nambi V, Christenson RH, Hashim IA, Hoogetveen RC, Ayers CR, Sun W, McGuire DK, Ballantyne CM, de Lemos JA. Age- and sex-dependent upper reference limits for the high-sensitivity cardiac troponin T assay. *J Am Coll Cardiol*. 2014;63:1441–1448. doi: 10.1016/j.jacc.2013.12.032.
 38. Sandoval Y, Apple FS. The global need to define normality: the 99th percentile value of cardiac troponin. *Clin Chem*. 2014;60:455–462. doi: 10.1373/clinchem.2013.211706.
 39. Artunc F, Mueller C, Breidhardt T, Twerenbold R, Peter A, Thamer C, Weyrich P, Haering HU, Friedrich B. Sensitive troponins: which suits better for hemodialysis patients? Associated factors and prediction of mortality. *PLoS One*. 2012;7:e47610. doi: 10.1371/journal.pone.0047610.

CLINICAL PERSPECTIVE

In this multicenter study, we examined the diagnostic performance and identified the optimal cutoff levels of 7 more sensitive cardiac troponin (cTn) assays for the early diagnosis of acute myocardial infarction (AMI) in patients with renal dysfunction. We report 7 novel findings that have important clinical implications for the early diagnosis of AMI in that they clearly highlight that more sensitive cTn assays maintain high diagnostic utility in patients with renal dysfunction as long as optimized cutoff levels are used. First, cTn levels at presentations, as assessed by all the more sensitive cTn assays, were significantly higher in patients whose final diagnosis was AMI compared with those with other final diagnoses. The prevalence of elevated cTn levels above the 99th percentile in patients with renal dysfunction and a final diagnosis other than AMI differed substantially among the 7 more sensitive cTn assays, ranging from 12% to 71%. Second, despite this, AMI remained the most common final diagnosis among patients with elevated cTn levels for all assays (range, 45%–80%). Third and perhaps most important, for all 7 more sensitive cTn assays, the diagnostic accuracy at presentation was high in patients with renal dysfunction and further increased for later sampling points. Diagnostic accuracy of the more sensitive cTn assays at presentation was only slightly lower compared with that in patients with normal renal function. Fourth, diagnostic accuracies were comparable among the 7 more sensitive cTn assays in patients with renal dysfunction with no systematic superiority of high-sensitivity cTn assays over sensitive assays. Fifth, at the 99th percentile, all cTn assays showed higher sensitivity but lower specificity in patients with renal dysfunction compared with patients with normal renal function, reflecting the higher baseline levels observed in patients with renal dysfunction even in the absence of AMI. Sixth, the receiver-operating characteristics curve–derived optimal cutoff levels in patients with renal dysfunction were 2- to 3-times higher in patients with renal dysfunction compared with patients with normal renal function. Seventh, cTn as measured with all 7 more sensitive cTn assays also retained prognostic value and predicted 2-year survival in patients with renal dysfunction.

Supplemental Material

Table of Contents

Supplemental Methods	2
Details on exclusion criteria	2
Use of hs-cTnT for adjudication of final diagnoses	2
Assumption of Linearity	3
Investigational Cardiac Troponin Analysis	3
Statistical Analysis	4
Supplemental Tables	7
Supplemental Figures	22
Supplemental References	26

Supplemental Methods

Details on exclusion criteria

For this analysis patients were excluded if the final diagnosis remained unclear after adjudication (n=92, 3%). The adjudication process for the final diagnosis assigns patients one out of five main diagnostic categories. AMI, unstable angina, cardiac disease other than CAD, non-cardiac disease, and unknown cause of acute chest pain. The latter is used if the clinical work-up performed was insufficient to allow the adjudicating cardiologists to reliably diagnose the final cause of acute chest pain. These patients remain in the analyses regarding the distinction of AMI yes/no (and counted as “no AMI”) as long as their hs-cTnT levels remain in the normal range during serial sampling, as at least one hs-cTnT level above the 99th percentile is required for a diagnosis of AMI according to the universal definition of AMI. In contrast, patients with an adjudicated diagnosis of “unclear cause” and at least one hs-cTnT level above the 99th percentile during serial sampling need to be excluded from this analysis as they can neither be reliably classified as “AMI” nor “no AMI”. This occurred in the above mentioned 92 (3%) patients.

Use of hs-cTnT for adjudication of final diagnoses

Adjudication of the final diagnosis was based on Roche hs-cTnT in order to take advantage of the higher sensitivity and higher overall diagnostic accuracy offered by hs-cTn assays. For hs-cTnT the 99th percentile of healthy individuals (14 ng/l) was used as cut-off for myocardial necrosis.^{1, 2}

Absolute changes in hs-cTnT were used to determine significant changes based on the diagnostic superiority of absolute over relative changes.^{3, 4} Based on studies of the

biological variation of cTn^{5, 6} as well as on data from previous chest pain cohort studies^{7, 8}, a significant absolute change was defined as a rise or fall of at least 10ng/l within six hours or an absolute change of 6 ng/l within three hours.

Assumption of Linearity

The assumption of linearity of absolute changes within the first hours is based on unpublished internal data as well as recent data from Hammarsten et al. showing a near-linear increase in levels of cTn with increasing time from symptom onset in their NSTEMI cohort.⁹

Investigational Cardiac Troponin Analysis

Blood samples for determination of cTn with the use of the three s-cTn assays (Abbott-Architect s-cTnI, Siemens Ultra s-cTnI and Beckman-Coulter Accu s-cTnI) and the four hs-cTn assays (Roche hs-cTnT, Abbott-Architect hs-cTnI, Siemens prototype hs-cTnI, Beckman-Coulter prototype hs-cTnI) were collected into tubes containing potassium EDTA- or heparin-plasma or serum at the time of the patient's presentation to the ED.¹⁰⁻¹⁶ Additional samples were collected at 1, 2, 3, and 6 hours. Serial sampling was discontinued when the diagnosis of AMI was certain and treatment required transferring the patient to the catheter laboratory or coronary care unit. After centrifugation, samples were frozen at -80°C until they were assayed in a blinded fashion in a dedicated core laboratory. The Abbott-Architect s-cTnI assay was performed with the use of the Architect system (Abbott Diagnostics), with a limit of detection (LoD) of 10 ng/l, a 99th percentile cut-off point of 28 ng/l, and a coefficient of variation (CV) of less than 10% at 32 ng/l.¹⁴ The Siemens Ultra s-

cTnI assay was performed with the use of the ADVIA Centaur immunoassay system (Siemens), with a LoD of 6 ng/l, a 99th percentile cut-off point of 40 ng/l, and a CV of less than 10% at 30 ng/l.^{7, 10, 11} The Beckman-Coulter Accu s-cTnI assay was measured on the Access 2 analyzer, with a LoD of 10 ng/l, a 99th percentile cut-off point of 42 ng/l, and a CV of less than 10% at 60 ng/l.^{14, 17, 18} The Roche hs-cTnT assays was performed with the use of the Elecsys 2010 system (Roche Diagnostics), with a LoD of 5 ng/l, a 99th-percentile cut-off point of 14 ng/l, and a CV of less than 10% at 13 ng/l.^{12, 13, 16} The Abbott-Architect hs-cTnI assay used was the final pre-commercial release version of the ARCHITECT High Sensitive *STAT* Troponin I assay (Abbott Laboratories, Abbott Park, IL). The Abbott-Architect hs-cTnI assay was performed with the use of the Architect system (Abbott Diagnostics) with a LoD of 1.9ng/l and a 99th percentile cut-off point of 26.2ng/L with a corresponding co-efficient of variation of <5%.¹⁹ The Siemens hs-cTnI assay, an experimental prototype assay, was performed with the use of the Dimension Vista® 1500 immunoassay system (Siemens), with a LoD of 0,5 ng/l, a 99th percentile cut-off point of 9 ng/l, and a CV of less than 10% at 3 ng/l.¹⁷ The Beckman-Coulter hs-cTnI assay was measured on the Access 2 analyzer using an investigational prototype assay. According to the manufacturer, LoD is 2 ng/l, the 99th percentile of a healthy reference population is 9.2 ng/l with a 10% CV lower than the 99th percentile.²⁰

Statistical Analysis

Continuous variables are presented as medians (with the corresponding first and third quartiles), and categorical variables as numbers and percentages. Continuous variables were compared with the use of the Mann–Whitney-test and Kruskal-Wallis-test, as appropriate, and categorical variables with the use of the Pearson-chi-square test.

Receiver-operating-characteristic (ROC) curves were constructed to assess the sensitivity and specificity of cTn measurements obtained at specific times with the seven more sensitive cTn-assays and to compare their ability to diagnose AMI. Logistic regression was used to combine cTn-levels at presentation with early changes in cTn-levels. The comparison of areas under the ROC curves (AUC) was performed as recommended by DeLong et al for dependent samples²¹ and by Hanley et al for independent samples.²² In order to compare the diagnostic accuracy across stages of renal dysfunction, MDRD GFR was divided into tertiles. The optimal ROC-derived cut-off levels were determined using the Youden-Index²³, defined by the minimal distance of the ROC-curve to the point (0;1) of the graph and compared to the 99th percentile of healthy individuals, as well as cut-off levels that achieve predefined sensitivities (90%, 95%) and specificities (80%, 90%). For this analysis, the 99th percentile of healthy individuals was chosen as in the diagnosis of AMI this cut-off level is universally recommend for clinical use by clinical practice guidelines and the universal definition of AMI.¹⁻⁴ These analyses were performed assay-specific using all patients with data for the respective assay in order to achieve the highest possible precision for our findings. We used the relevant cross table at this cut-off point to calculate diagnostic performance parameters and its 95% confidence interval.²⁴ In case of independent binary outcomes we used the χ^2 -Test to compare sensitivity, specificity, positive and negative predictive value. Correlations between renal function and levels of cTn at presentation were determined with the use of Pearson rank correlation. For the analysis of the prognostic value of the cTn assays we did Kaplan-Meier analysis and presented cumulative survival rates at two years. Furthermore, we performed a separate Cox regression analysis for each assay including the elevated levels of cTn above the ROC-derived optimal diagnostic cut-off level, age, gender, arterial hypertension, hypercholesterolaemia, pre-existing coronary artery disease and estimated glomerular filtration rate at presentation. All hypothesis testing

was two-tailed, and P values of less than 0.05 were considered to indicate statistical significance without adjustments for multiple testing. All statistical analyses were performed with the use of IBM SPSS Statistics for Windows, version 22.0 (SPSS Inc Chicago, IL), and MedCalc software, version 14.8.1 (MedCalc, Ostend, Belgium).

Supplemental Tables

Supplemental Table 1. Distribution of Baseline Characteristics Among the Seven Assay-specific Cohorts.

	Abbott-Architect s-cTnI	Siemens Ultra s-cTnI	Beckman-Coulter Accu s-cTnI	Roche hs-cTnT	Abbot-Architect hs-cTnI	Siemens hs-cTnI	Beckman-Coulter hs-cTnI	p-value [†]
Cohort size - no. (%)	1314 (100)	2663 (100)	1154 (100)	2813 (100)	2287 (100)	1874 (100)	1154 (100)	-
Male gender – no. (%)	877 (67)	1811 (68)	768 (67)	1907 (68)	1549 (68)	1259 (67)	768 (67)	0.936
Age – median (Q1, Q3) – years	63 (51, 75)	62 (49, 74)	63 (50, 75)	62 (49, 74)	62 (49, 75)	62 (49, 74)	63 (50, 75)	0.057
Cardiovascular Risk Factors – no. (%)								
Diabetes mellitus	243 (19)	462 (18)	212 (18)	488 (17)	399 (18)	323 (17)	212 (18)	0.951
Current smoking	333 (25)	683 (26)	282 (24)	720 (26)	585 (26)	473 (25)	282 (24)	0.754
History of smoking	463 (35)	966 (36)	404 (35)	1013 (36)	821 (36)	671 (36)	404 (35)	0.773
Hypercholesterolemia	661 (50)	1340 (50)	580 (50)	1407 (50)	1142 (50)	933 (50)	580 (50)	1.000
Hypertension	853 (65)	1647 (62)	765 (66)	1741 (62)	1426 (62)	1166 (62)	765 (66)	0.011
History – no. (%)								
Coronary artery disease	459 (35)	918 (35)	413 (36)	965 (34)	790 (35)	639 (34)	413 (36)	0.936
Previous myocardial infarction	307 (23)	621 (23)	280 (24)	653 (23)	522 (23)	439 (23)	280 (24)	0.963
Previous revascularization	342 (26)	733 (28)	312 (27)	768 (27)	681 (27)	512 (27)	312 (27)	0.981
Peripheral artery disease	90 (7)	158 (6)	78 (7)	171 (6)	145 (6)	107 (6)	78 (7)	0.758
Previous stroke	68 (5)	146 (6)	66 (6)	154 (6)	126 (6)	107 (6)	66 (6)	0.996
ECG Findings – no. (%)								
ST segment elevation	75 (6)	129 (5)	61 (6)	134 (5)	101 (4)	86 (5)	61 (5)	0.643
ST segment depression	164 (13)	302 (11)	139 (12)	322 (11)	266 (12)	197 (11)	139 (12)	0.703
T-wave inversion	179 (14)	357 (13)	153 (13)	375 (13)	313 (14)	231 (12)	153 (13)	0.921
Left bundle branch block	46 (4)	73 (3)	40 (4)	81 (3)	69 (3)	57 (3)	40 (4)	0.760

Supplemental Table 1 (continued). Distribution of Baseline Characteristics Among the Seven Assay-specific Cohorts.

	Abbott-Architect s-cTnI	Siemens Ultra s-cTnI	Beckman-Coulter Accu s-cTnI	Roche hs-cTnT	Abbot-Architect hs-cTnI	Siemens hs-cTnI	Beckman-Coulter hs-cTnI	p-value [†]
Cohort size - no. (%)	1314 (100)	2663 (100)	1154 (100)	2813 (100)	2287 (100)	1874 (100)	1154 (100)	-
Diagnostic Exams and Interventions* – no. (%)								
Coronary angiographies	359 (27)	697 (26)	313 (27)	739 (26)	596 (26)	491 (26)	313 (27)	0.963
Coronary interventions	214 (16)	418 (16)	189 (16)	443 (16)	350 (15)	294 (16)	189 (16)	0.973
CABG	35 (3)	60 (2)	32 (3)	64 (2)	55 (3)	46 (3)	32 (3)	0.913
Renal Function – median (Q1, Q3)								
Creatinine – µmol/l	76 (65, 91)	76 (65, 89)	75 (64, 91)	76 (65, 90)	76 (64, 90)	76 (65, 89)	75 (64, 91)	1.000
MDRD GFR – ml/min/1.73m ²	84 (67, 100)	85 (69, 101)	85 (68, 101)	85 (69, 101)	85 (69, 101)	85 (69, 100)	85 (68, 101)	0.893
Renal Dysfunction [†] - no (%)								
	219 (17)	416 (16)	190 (17)	447 (16)	366 (16)	283 (15)	190 (17)	0.902
Stages of Renal Dysfunction - no (%)								
eGFR 30-59ml/min/1.73m ²	195 (15)	375 (14)	169 (15)	403 (14)	330 (14)	253 (14)	169 (15)	1.000
eGFR 15-29ml/min/1.73m ²	19 (1)	31 (1)	17 (2)	34 (1)	28 (1)	24 (1)	17 (2)	
eGFR <15ml/min/1.73m ²	5 (0.4)	10 (0.4)	4 (0.3)	10 (0.4)	8 (0.3)	6 (0.3)	4 (0.3)	
Final Diagnosis – no (%)								
Acute Myocardial Infarction	272 (21)	546 (21)	230 (20)	573 (20)	470 (21)	355 (19)	230 (20)	0.866
STEMI	52 (4)	97 (4)	47 (4)	103 (4)	73 (3)	72 (4)	47 (4)	
NSTEMI	220 (17)	449 (17)	183 (16)	470 (17)	397 (17)	283 (15)	183 (16)	

** performed during or directly after the index visit (within 1 month after discharge).*

† Renal dysfunction was diagnosed if the estimated MDRD glomerular filtration rate was $<60\text{ml/min/1.73m}^2$ at presentation.

‡ χ^2 -test used for comparison of proportions, Kruskal-Wallis-test used for comparison of the distribution of continuous variables between the seven cohorts

Q1 denotes the first quartile, Q3 the third quartile.

Supplemental Table 2. Distribution of the adjudicated final diagnoses.

	All patients (n=2813)	Normal Renal Function (n=2366)	Renal Dysfunction (n=447)	p-value[†]
Acute myocardial infarction	573 (20%)	413 (18%)	160 (36%)	<0.001
- ST segment elevation	103 (4%)	83 (4%)	20 (5%)	0.319

- Non-ST segment elevation	470 (17%)	330 (14%)	140 (31%)	<0.001
- Type 1	405 (14%)	297 (13%)	108 (24%)	<0.001
- Type 2	65 (2%)	33 (1%)	32 (7%)	<0.001
Unstable Angina	269 (10%)	219 (9%)	50 (11%)	0.203
Cardiac cause, but not CAD*	396 (13%)	312 (13%)	84 (19%)	0.002
Noncardiac cause	1445 (51%)	1305 (55%)	140 (31%)	<0.001
Unknown	130 (5%)	117 (5%)	13 (3%)	0.060

*CAD denotes coronary artery disease

† χ^2 -test for comparison of proportions of patients with renal dysfunction and normal renal function.

Supplemental Table 3A. Median Absolute Changes of High-Sensitivity Cardiac Troponin T During Serial Sampling Among Patients with Acute Myocardial Infarction (n=573).

Absolute change of Roche hs-cTnT (ng/l) – median (Q1 - Q3)	Normal renal function (n=413)	Renal dysfunction (n=160)	p-value
Delta 0-1h	10.9 (4.0, 36)	8.0 (3.0, 27.5)	0.354
Delta 0-2h	22.5 (7, 68)	11.6 (5.0, 39.5)	0.034
Delta 0-3h	29.0 (8.9, 90)	22.5 (6.2, 97.9)	0.584

Delta 0-6h	36.1 (13.6, 175.0)	39.5 (8.9, 166.0)	0.797
Delta 0h-Peak	55.0 (22.0, 161.8)	64.7 (37.9, 166.3)	0.012

Q1 denotes the first quartile, Q3 the third quartile.

Supplemental Table 3B. Distribution of Absolute Changes of High-Sensitivity Cardiac Troponin T During Serial Sampling Among Patients with Acute Myocardial Infarction (n=573).

Absolute change of Roche hs-cTnT - n (%)	Normal renal function	Renal dysfunction	p-value
	(n=413)	(n=160)	
Delta 0h-Peak < 10 ng/l	36 (9%)	3 (2%)	0.006
Delta 0h-Peak < 20 ng/l	91 (22%)	17 (11%)	0.004
Delta 0h-Peak ≥ 20 and <100ng/l	126 (31%)	77 (48%)	<0.001
Delta 0h-Peak > 100 ng/l	142 (34%)	57 (36%)	0.724
Delta 0h-Peak > 1000 ng/l	18 (4%)	6 (4%)	0.812

Supplemental Table 4. Diagnostic Accuracy of Cardiac Troponin in Patients with Renal Dysfunction at Serial Sampling (Area under the Curve, 95%CI).

		Presentation	1 hour	2 hours	3 hours
Sensitive Cardiac Troponin Assays					
Abbott-Architect s-cTnI	AUC	0.89 (0.85-0.94)	0.91 (0.86-0.96)	0.91 (0.86-0.96)	0.94 (0.90-0.99)
	n	219	152	117	101
Siemens Ultra s-cTnI	AUC	0.87 (0.84-0.91)	0.90 (0.87-0.94)	0.91 (0.87-0.95)	0.94 (0.90-0.98)
	n	416	317	244	118

Beckman-Coulter Accu s-cTnl	AUC n	0.89 (0.84-0.94) 190	0.92 (0.87-0.97) 147	0.93 (0.88-0.98) 108	0.95 (0.91-0.99) 100
High-Sensitivity Cardiac Troponin Assays					
Roche hs-cTnT	AUC n	0.87 (0.84-0.91) 447	0.90 (0.86-0.93) 341	0.91 (0.87-0.94) 270	0.94 (0.90-0.98) 150
Abbott-Architect hs-cTnl	AUC n	0.87 (0.83-0.91) 366	0.89 (0.85-0.93) 277	0.90 (0.86-0.95) 206	0.93 (0.87-.98) 108
Siemens hs-cTnl	AUC n	0.89 (0.84-0.94) 283	0.92 (0.87-0.96) 223	0.91 (0.86-0.97) 174	0.91 (0.83-0.99) 105
Beckman-Coulter hs-cTnl	AUC n	0.89 (0.84-0.94) 190	0.92 (0.88-0.97) 147	0.93 (0.89-0.98) 108	0.94 (0.89-0.98) 100

AUC denotes area under the receiver operating characteristic curve.

Supplemental Table 5. Diagnostic Accuracy of Absolute Values of Early Changes ($|\Delta 1h-0h|$ and $|\Delta 2h-0h|$) in Cardiac Troponin and the Combination of the cardiac Troponin Level at Presentation with Early Changes during Serial Sampling (Area under the Curve, 95%CI).

		0h	$ \Delta 1h-0h $	0h plus $ \Delta 1h-0h $	$ \Delta 2h-0h $	0h plus $ \Delta 2h-0h $
Sensitive Cardiac Troponin Assays						
Abbott-Architect s-cTnI	AUC	0.89 (0.85-0.94)	0.88 (0.81-0.94)	0.90 (0.85-0.95)	0.88 (0.80-0.95)	0.89 (0.82-0.95)
	n	219	152	152	117	117
Siemens Ultra s-cTnI	AUC	0.87 (0.84-0.91)	0.87 (0.82-0.91)	0.90 (0.86-0.93)	0.88 (0.83-0.93)	0.90 (0.85-0.94)
	n	416	317	317	244	244
Beckman-Coulter Accu s-cTnI	AUC	0.89 (0.84-0.94)	0.90 (0.83-0.96)	0.91 (0.85-0.96)	0.92 (0.85-0.99)	0.89 (0.81-0.98)
	n	190	147	147	108	108
High-Sensitivity Cardiac Troponin Assays						
Roche hs-cTnT	AUC	0.87 (0.84-0.91)	0.90 (0.86-0.94)	0.93 (0.90-0.96)	0.88 (0.83-0.93)	0.89 (0.85-0.93)
	n	447	341	341	270	270
Abbott-Architect hs-cTnI	AUC	0.87 (0.83-0.91)	0.90 (0.86-0.94)	0.90 (0.86-0.94)	0.92 (0.88-0.96)	0.91 (0.87-0.95)
	n	366	277	277	206	206
Siemens hs-cTnI	AUC	0.89 (0.84-0.94)	0.90 (0.84-0.95)	0.92 (0.88-0.97)	0.91 (0.86-0.97)	0.92 (0.86-0.97)
	n	283	223	223	174	174
Beckman-Coulter hs-cTnI	AUC	0.89 (0.84-0.94)	0.89 (0.82-0.96)	0.91 (0.85-0.96)	0.94 (0.89-0.99)	0.90 (0.84-0.97)
	n	190	147	147	108	108

AUC denotes Area under the receiver operating characteristic curve.

Supplemental Table 6. Diagnostic accuracy of cardiac troponin at presentation in patients with renal dysfunction stratified by tertiles of glomerular filtration rate (Area under the Curve, 95%CI)*.

	n	Tertiles of GFR*	AUC [†] (95% CI)	p-value (for comparisons with lowest tertile)
Sensitive Cardiac Troponin Assays				
Abbott-Architect s-cTnI	219	Highest tertile	0.91 (0.84-0.98)	0.204
		Intermediate tertile	0.94 (0.89-1.00)	0.057
		Lowest tertile	0.83 (0.73-0.93)	-
Siemens Ultra s-cTnI	416	Highest tertile	0.87 (0.80-0.94)	0.412
		Intermediate tertile	0.93 (0.86-0.96)	0.022
		Lowest tertile	0.83 (0.77-0.90)	-
Beckman-Coulter Accu s-cTnI	190	Highest tertile	0.90 (0.80-1.00)	0.424
		Intermediate tertile	0.94 (0.89-1.00)	0.105
		Lowest tertile	0.84 (0.73-0.95)	-
High-Sensitivity Cardiac Troponin Assays				
Roche hs-cTnT	447	Highest tertile	0.89 (0.83-0.95)	0.062
		Intermediate tertile	0.90 (0.85-0.95)	0.024
		Lowest tertile	0.80 (0.73-0.87)	-
Abbott-Architect hs-cTnI	366	Highest tertile	0.88 (0.81-0.95)	0.193
		Intermediate tertile	0.91 (0.86-0.96)	0.038
		Lowest tertile	0.81 (0.74-0.89)	-
Siemens hs-cTnI	283	Highest tertile	0.91 (0.85-0.98)	0.267
		Intermediate tertile	0.92 (0.84-0.99)	0.222
		Lowest tertile	0.85 (0.76-0.93)	-
Beckman-Coulter hs-cTnI	190	Highest tertile	0.90 (0.81-0.99)	0.417
		Intermediate tertile	0.95 (0.90-1.00)	0.077
		Lowest tertile	0.84 (0.72-0.95)	-

* eGFR denotes estimated glomerular filtration rate. Highest tertile >53 ml/min/1.73m², intermediate tertile 53 to >42 ml/min/1.73m², lowest tertile ≤42ml/min/1.73m².

† AUC denotes Area under the receiver operating characteristic curve.

Supplemental Table 7A. Diagnostic performance of cardiac troponin in renal dysfunction at presentation.

Assay	Cut-off level (ng/l)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)	Multiples of the 99 th Percentile	Multiples RD vs. no RD
Sensitive Cardiac Troponin Assays							
Abbott-Architect s-cTnI (n=219)							
99 th percentile	28 ng/l	79 (69-88)	89 (82-93)	89 (82-93)	79 (69-88)	-	-
Specificity optimized cut-off (≥90%)	39 ng/l	67 (55-77)	90 (84-94)	83 (76-89)	79 (67-88)	1.4	3.3
Specificity optimized cut-off (≥80%)	17 ng/l	81 (70-89)	80 (73-86)	88 (81-93)	69 (59-78)	0.6	4.3
ROC-optimized cut-off	27 ng/l	79 (69-88)	87 (81-92)	88 (82-93)	78 (67-86)	1.0	3.4
Sensitivity optimized cut-off (≥90%)	12 ng/l	91 (82-96)	70 (61-77)	93 (87-97)	62 (53-71)	0.4	6.0
Sensitivity optimized cut-off (≥95%)	6 ng/l	96 (89-99)	52 (44-61)	96 (89-99)	53 (44-61)	0.2	n.a.
Limit of Detection	10 ng/l	91 (82-96)	65 (56-72)	93 (86-97)	59 (49-68)	0.4	-
Siemens Ultra s-cTnI (n=416)							
99 th percentile	40 ng/l	79 (72-85)	81 (75-85)	87 (83-91)	69 (63-76)	-	-
Specificity optimized cut-off (≥90%)	62 ng/l	70 (62-77)	90 (85-93)	84 (79-88)	79 (71-85)	1.6	2.5
Specificity optimized cut-off (≥80%)	38 ng/l	80 (73-86)	80 (75-85)	88 (83-92)	69 (62-76)	1.0	2.9
ROC-optimized cut-off	46 ng/l	77 (70-84)	84 (79-88)	87 (82-91)	73 (66-80)	1.2	2.4
Sensitivity optimized cut-off (≥90%)	17 ng/l	91 (86-95)	55 (49-61)	92 (87-96)	53 (47-60)	0.4	1.3
Sensitivity optimized cut-off (≥95%)	10 ng/l	96 (91-99)	42 (36-48)	95 (89-98)	48 (42-54)	0.3	1.4
Limit of Detection	6 ng/l	99 (95-100)	27 (21-32)	97 (90-100)	43 (38-48)	0.2	-
Beckman-Coulter Accu s-cTnI (n=190)							
99 th percentile	42 ng/l	79 (67-89)	88 (81-93)	90 (83-94)	77 (65-86)	-	-
Specificity optimized cut-off (≥90%)	53 ng/l	73 (60-83)	91 (84-95)	87 (80-92)	79 (67-89)	1.3	2.4
Specificity optimized cut-off (≥80%)	28 ng/l	84 (73-92)	80 (71-86)	91 (84-96)	67 (56-77)	0.7	2.5
ROC-optimized cut-off	36 ng/l	81 (69-90)	88 (81-93)	90 (84-95)	77 (65-87)	0.9	2.1
Sensitivity optimized cut-off (≥90%)	18 ng/l	90 (80-96)	66 (57-74)	93 (86-98)	57 (47-67)	0.4	1.8
Sensitivity optimized cut-off (≥95%)	15 ng/l	95 (87-99)	57 (48-65)	96 (89-99)	52 (43-62)	0.4	3.0
Limit of Detection	10 ng/l	95 (87-99)	44 (35-53)	95 (86-99)	46 (37-55)	0.2	-

Supplemental Table 7A (continued). Diagnostic performance of cardiac troponin in renal dysfunction at presentation.

Assay	Cut-off level (ng/l)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)	Multiples of the 99 th Percentile	Multiples RD vs. no RD
High-Sensitivity Cardiac Troponin Assays							
Roche hs-cTnT (n=447)							
99 th percentile	14.0 ng/l	98 (94-99)	32 (27-38)	96 (90-99)	45 (39-50)	-	-
Specificity optimized cut-off (≥90%)	51.1 ng/l	61 (53-68)	90 (86-93)	80 (76-85)	77 (69-84)	3.7	3.0
Specificity optimized cut-off (≥80%)	31.8 ng/l	81 (74-87)	80 (74-84)	88 (84-92)	69 (62-75)	2.3	2.7
ROC-optimized cut-off	29.5 ng/l	84 (77-89)	79 (74-83)	90 (85-93)	69 (62-75)	2.1	1.9
Sensitivity optimized cut-off (≥90%)	20.9 ng/l	91 (85-95)	59 (53-64)	92 (87-95)	55 (49-61)	1.5	1.7
Sensitivity optimized cut-off (≥95%)	16.0 ng/l	97 (93-99)	41 (35-47)	96 (91-99)	48 (42-53)	1.1	1.8
Limit of Detection	5.0 ng/l	100 (98-100)	3 (1-5)	100 (63-100)	36 (32-41)	0.4	-
Abbott-Architect hs-cTnI (n=366)							
99 th percentile	26.2 ng/l	77 (69-84)	83 (78-88)	86 (80-90)	74 (66-81)	-	-
Specificity optimized cut-off (≥90%)	42.6 ng/l	68 (60-76)	90 (85-93)	82 (77-87)	81 (72-87)	1.6	3.0
Specificity optimized cut-off (≥80%)	23.3 ng/l	78 (71-85)	80 (74-85)	86 (80-90)	70 (62-77)	0.9	3.2
ROC-optimized cut-off	29.4 ng/l	76 (68-82)	85 (80-89)	85 (80-89)	76 (68-82)	1.1	2.6
Sensitivity optimized cut-off (≥90%)	8.8 ng/l	91 (85-95)	48 (42-55)	89 (83-94)	52 (45-58)	0.3	1.0
Sensitivity optimized cut-off (≥95%)	6.9 ng/l	96 (92-99)	39 (33-46)	95 (88-98)	49 (43-55)	0.3	1.1
Limit of Detection	1.9 ng/l	100 (97-100)	3 (1-6)	100 (54-100)	39 (34-44)	0.1	-
Siemens hs-cTnI (n=283)							
99 th percentile	9.0 ng/l	94 (86-98)	56 (49-63)	95 (89-98)	51 (43-59)	-	-
Specificity optimized cut-off (≥90%)	60.2 ng/l	74 (64-83)	90 (85-94)	88 (82-92)	78 (68-87)	6.7	2.3
Specificity optimized cut-off (≥80%)	27.6 ng/l	82 (72-89)	80 (74-85)	90 (84-94)	67 (57-75)	3.1	2.7
ROC-optimized cut-off	32.0 ng/l	82 (72-89)	83 (77-88)	90 (85-94)	70 (61-79)	3.6	2.5
Sensitivity optimized cut-off (≥90%)	16.1 ng/l	90 (82-95)	71 (63-77)	94 (88-97)	60 (51-68)	1.8	1.2
Sensitivity optimized cut-off (≥95%)	5.9 ng/l	96 (89-99)	42 (35-49)	95 (88-99)	45 (37-52)	0.7	0.9
Limit of Detection	0.5 ng/l	99 (94-100)	4 (2-8)	89 (52-100)	34 (28-40)	0.1	-
Beckman-Coulter hs-cTnI (n=190)							
99 th percentile	9.2 ng/l	95 (87-99)	48 (39-57)	95 (87-99)	48 (39-57)	-	-
Specificity optimized cut-off (≥90%)	47.1 ng/l	71 (59-82)	90 (83-94)	86 (79-92)	78 (65-87)	5.1	2.7
Specificity optimized cut-off (≥80%)	22.4 ng/l	84 (73-92)	80 (71-86)	91 (84-96)	67 (56-77)	2.4	2.4
ROC-optimized cut-off	25.9 ng/l	81 (69-90)	83 (76-89)	90 (83-95)	71 (59-81)	2.8	2.3
Sensitivity optimized cut-off (≥90%)	14.6 ng/l	90 (80-96)	68 (59-75)	93 (86-98)	58 (48-68)	1.6	1.6
Sensitivity optimized cut-off (≥95%)	10.9 ng/l	95 (87-99)	57 (48-66)	96 (89-99)	53 (43-62)	1.2	1.8
Limit of Detection	2.1 ng/l	100 (94-100)	3 (1-8)	100 (40-100)	34 (27-41)	0.2	-

Supplemental Table 7B. Diagnostic performance of cardiac troponin in normal renal function at presentation.

Assay	Cut-off level (ng/l)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)	Multiples of the 99 th Percentile
Sensitive Cardiac Troponin Assays						
Abbott-Architect s-cTnI (n=1095)						
99 th percentile	28 ng/l	70 (63-76)	94 (92-95)	93 (92-95)	71 (64-77)	-
Specificity optimized cut-off (≥90%)	12 ng/l	79 (72-84)	90 (88-92)	95 (94-97)	62 (56-68)	0.4
Specificity optimized cut-off (≥80%)	4 ng/l	85 (79-90)	80 (76-82)	96 (94-97)	47 (42-52)	0.1
ROC-optimized cut-off	8 ng/l	84 (78-89)	85 (83-87)	96 (95-97)	55 (49-60)	0.3
Sensitivity optimized cut-off (≥90%)	2 ng/l	92 (86-95)	68 (65-71)	97 (96-99)	38 (34-43)	0.1
Sensitivity optimized cut-off (≥95%)	<1 ng/l	100 (98-100)	n.a.	n.a.	18 (16-20)	n.a.
Limit of Detection	10 ng/l	81 (75-87)	88 (85-90)	96 (94-97)	59 (52-64)	0.4
Siemens Ultra s-cTnI (n=2247)						
99 th percentile	40 ng/l	75 (70-79)	94 (92-95)	94 (93-95)	71 (67-76)	-
Specificity optimized cut-off (≥90%)	25 ng/l	81 (77-85)	90 (89-91)	96 (95-97)	64 (59-68)	0.6
Specificity optimized cut-off (≥80%)	13 ng/l	90 (87-93)	80 (78-82)	97 (96-98)	49 (45-53)	0.3
ROC-optimized cut-off	19 ng/l	88 (84-91)	86 (84-87)	97 (96-98)	56 (52-60)	0.5
Sensitivity optimized cut-off (≥90%)	13 ng/l	90 (87-93)	79 (77-80)	97 (96-98)	47 (44-51)	0.3
Sensitivity optimized cut-off (≥95%)	7 ng/l	95 (93-97)	61 (59-63)	98 (98-99)	35 (32-37)	0.2
Limit of Detection	6 ng/l	96 (94-98)	57 (55-59)	99 (98-99)	33 (30-35)	0.2
Beckman-Coulter Accu s-cTnI (n=964)						
99 th percentile	42 ng/l	69 (61-76)	94 (92-95)	94 (92-95)	70 (62-77)	-
Specificity optimized cut-off (≥90%)	22 ng/l	79 (72-85)	90 (88-92)	95 (94-97)	62 (55-69)	0.5
Specificity optimized cut-off (≥80%)	11 ng/l	89 (84-93)	79 (76-82)	97 (96-98)	47 (42-53)	0.3
ROC-optimized cut-off	17 ng/l	83 (77-89)	88 (85-90)	96 (94-97)	58 (52-65)	0.4
Sensitivity optimized cut-off (≥90%)	10 ng/l	90 (84-94)	77 (74-80)	97 (96-98)	45 (40-51)	0.2
Sensitivity optimized cut-off (≥95%)	5 ng/l	95 (91-98)	55 (51-58)	98 (96-99)	31 (27-35)	0.1
Limit of Detection	10 ng/l	90 (84-94)	77 (74-80)	97 (96-98)	45 (40-51)	0.2

Supplemental Table 7B (continued). Diagnostic performance of cardiac troponin in normal renal function at presentation.

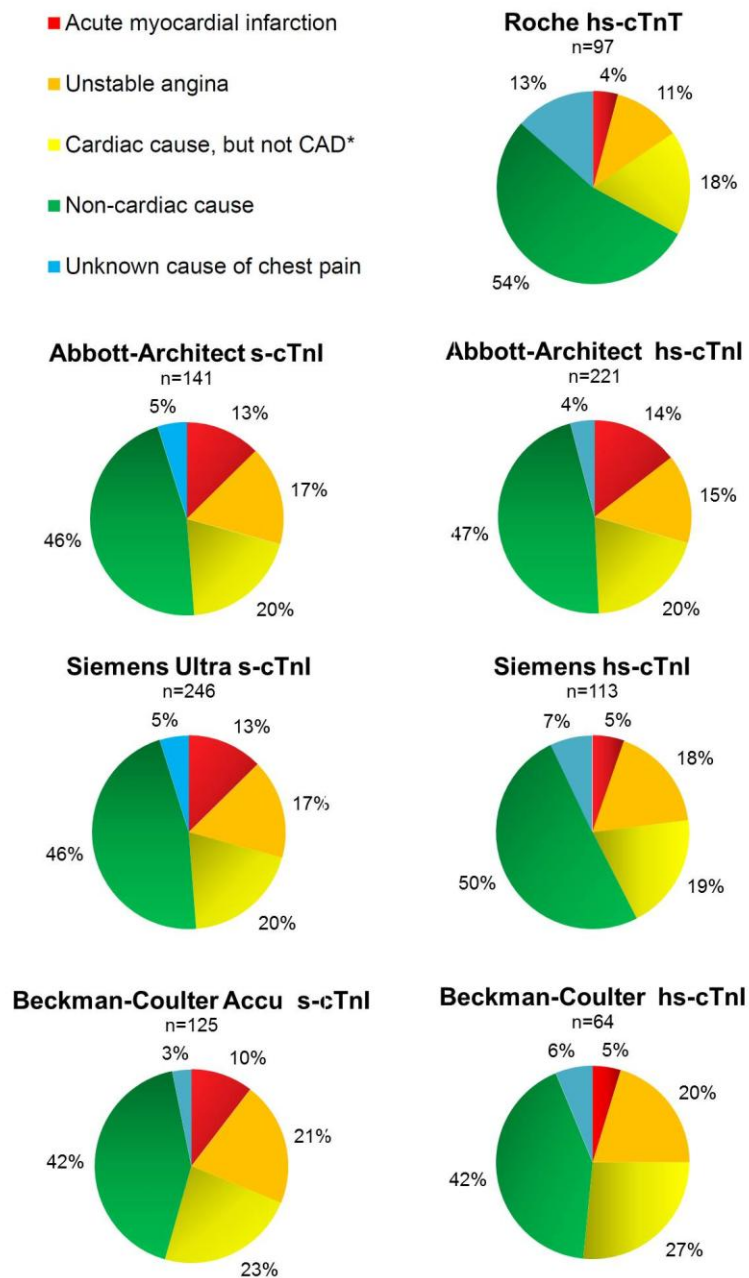
Assay	Cut-off level (ng/l)	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)	Multiples of the 99 th Percentile
High-Sensitivity Cardiac Troponin Assays						
Roche hs-cTnT (n=2366)						
99 th percentile	14.0 ng/l	88 (84-91)	86 (84-87)	97 (96-98)	56 (52-60)	-
Specificity optimized cut-off (≥90%)	16.9 ng/l	84 (80-87)	90 (88-91)	96 (95-97)	63 (59-67)	1.2
Specificity optimized cut-off (≥80%)	11.9 ng/l	91 (88-94)	80 (78-81)	98 (97-98)	49 (45-52)	0.9
ROC-optimized cut-off	15.9 ng/l	85 (81-89)	88 (87-90)	97 (96-97)	61 (57-65)	1.1
Sensitivity optimized cut-off (≥90%)	12.3 ng/l	90 (87-93)	82 (80-83)	98 (97-98)	51 (47-55)	0.9
Sensitivity optimized cut-off (≥95%)	8.9 ng/l	95 (93-97)	67 (65-69)	99 (98-99)	38 (35-41)	0.6
Limit of Detection	5.0 ng/l	100 (98-100)	34 (32-36)	100 (99-100)	24 (22-26)	0.4
Abbott-Architect hs-cTnI (n=1921)						
99 th percentile	26.2 ng/l	71 (66-76)	94 (93-95)	94 (93-95)	71 (66-76)	-
Specificity optimized cut-off (≥90%)	14.3 ng/l	82 (77-86)	90 (88-91)	96 (95-97)	63 (58-68)	0.5
Specificity optimized cut-off (≥80%)	7.3 ng/l	93 (89-95)	80 (78-82)	98 (97-99)	49 (45-53)	0.3
ROC-optimized cut-off	11.4 ng/l	87 (83-90)	87 (85-89)	97 (96-98)	58 (53-62)	0.4
Sensitivity optimized cut-off (≥90%)	8.8 ng/l	90 (87-93)	83 (81-85)	98 (97-98)	53 (49-57)	0.3
Sensitivity optimized cut-off (≥95%)	6.2 ng/l	95 (92-97)	76 (74-78)	99 (98-99)	45 (41-49)	0.2
Limit of Detection	1.9 ng/l	100 (99-100)	18 (16-20)	100 (99-100)	20 (18-22)	0.1
Siemens hs-cTnI (n=1591)						
99 th percentile	9.0 ng/l	93 (89-96)	78 (75-90)	98 (97-99)	45 (41-49)	-
Specificity optimized cut-off (≥90%)	25.9 ng/l	77 (71-82)	90 (88-92)	95 (94-96)	60 (55-65)	2.9
Specificity optimized cut-off (≥80%)	10.1 ng/l	92 (88-95)	80 (78-82)	98 (97-99)	47 (43-52)	1.1
ROC-optimized cut-off	12.9 ng/l	90 (86-94)	84 (82-86)	98 (97-99)	52 (48-57)	1.4
Sensitivity optimized cut-off (≥90%)	13.0 ng/l	90 (86-94)	84 (82-86)	98 (97-99)	52 (48-57)	1.4
Sensitivity optimized cut-off (≥95%)	6.4 ng/l	95 (92-97)	71 (69-74)	99 (98-99)	40 (36-44)	0.7
Limit of Detection	0.5 ng/l	100 (98-100)	16 (15-19)	100 (97-100)	19 (17-21)	0.1
Beckman-Coulter hs-cTnI (n=964)						
99 th percentile	9.2 ng/l	90 (85-94)	80 (77-82)	98 (6-99)	48 (43-54)	-
Specificity optimized cut-off (≥90%)	17.7 ng/l	80 (73-85)	90 (88-92)	95 (94-97)	62 (56-69)	1.9
Specificity optimized cut-off (≥80%)	9.3 ng/l	90 (84-94)	80 (77-83)	97 (96-98)	48 (43-54)	1.0
ROC-optimized cut-off	11.1 ng/l	88 (82-93)	84 (81-86)	97 (96-98)	53 (47-59)	1.2
Sensitivity optimized cut-off (≥90%)	9.2 ng/l	90 (85-94)	80 (77-82)	98 (96-99)	48 (43-54)	1.0
Sensitivity optimized cut-off (≥95%)	5.9 ng/l	95 (91-98)	67 (63-70)	99 (97-99)	37 (33-42)	0.6
Limit of Detection	2.1 ng/l	99 (97-100)	17 (14-20)	99 (96-100)	20 (17-23)	0.2

Supplemental Table 8. Predictive value of elevated cardiac troponin values above the ROC-optimized cut-off level for two-year mortality in patients with renal dysfunction.

	Cut-off level	Univariable Regression Model		Multivariable Regression Model*	
		Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Sensitive Cardiac Troponin Assays					
Abbott-Architect s-cTnI	≥ 27 ng/l	2.5 (1.4-4.4)	0.002	2.2 (1.3-3.9)	0.006
Siemens Ultra s-cTnI	≥ 46 ng/l	2.5 (1.6-3.9)	<0.001	2.3 (1.5-3.5)	<0.001
Beckman-Coulter Accu s-cTnI	≥ 36 ng/l	2.7 (1.5-5.0)	0.001	2.6 (1.4-4.9)	0.002
High-Sensitivity Cardiac Troponin Assays					
Roche hs-cTnT	≥ 29.5 ng/l	3.0 (2.0-4.6)	<0.001	2.2 (1.4-3.5)	<0.001
Abbott-Architect hs-cTnI	≥ 29.4 ng/l	2.3 (1.5-3.6)	<0.001	2.1 (1.4-3.3)	0.001
Siemens hs-cTnI	≥ 32.0 ng/l	1.6 (1.0-2.8)	0.067	1.6 (0.9-2.8)	0.082
Beckman-Coulter hs-cTnI	≥ 25.9 ng/l	2.3 (1.3-4.3)	0.006	2.3 (1.2-4.2)	0.009

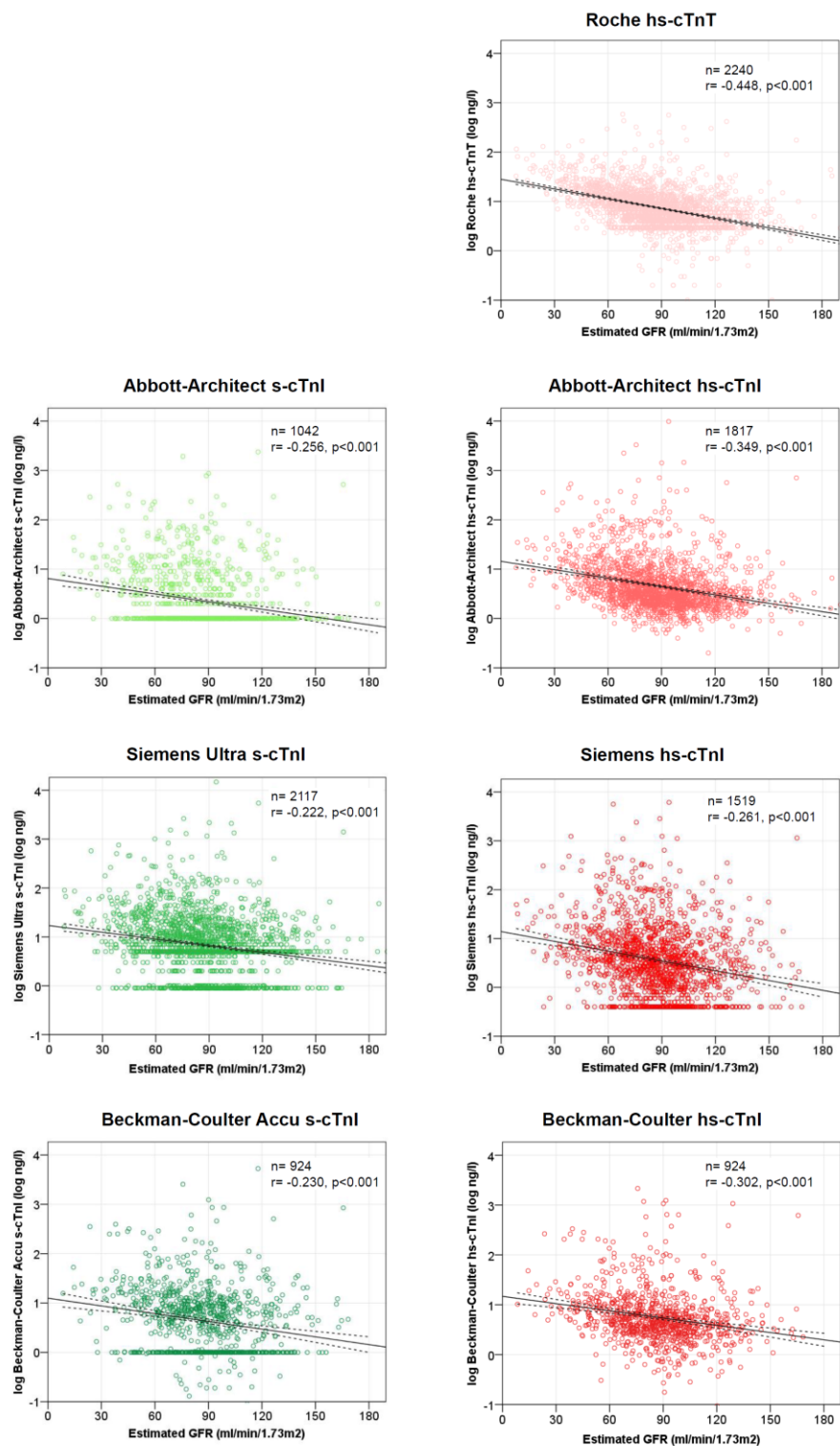
* adjusted for age, gender, pre-existing coronary artery disease, arterial hypertension, hypercholesterolaemia and estimated glomerular filtration rate using MDRD-formula based on creatinine-measurement at presentation.

Supplemental Figures



Supplemental Figure 1 Distribution of final diagnoses in patients with renal dysfunction and normal cardiac troponin at presentation.

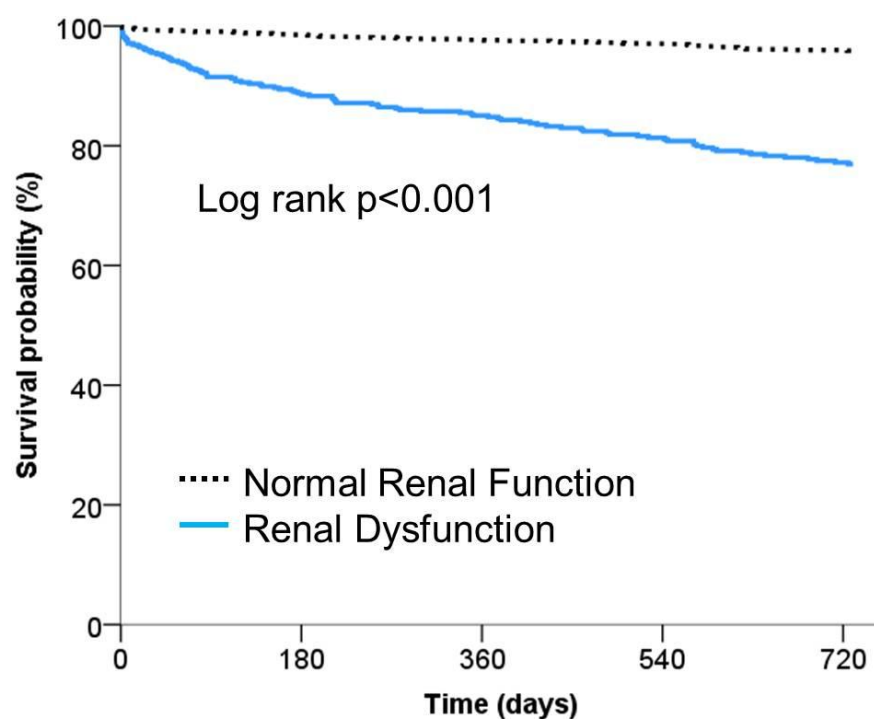
* CAD denotes coronary artery disease



**Supplemental
Figure 2**

Correlations between glomerular filtration rate and levels of cardiac troponin.

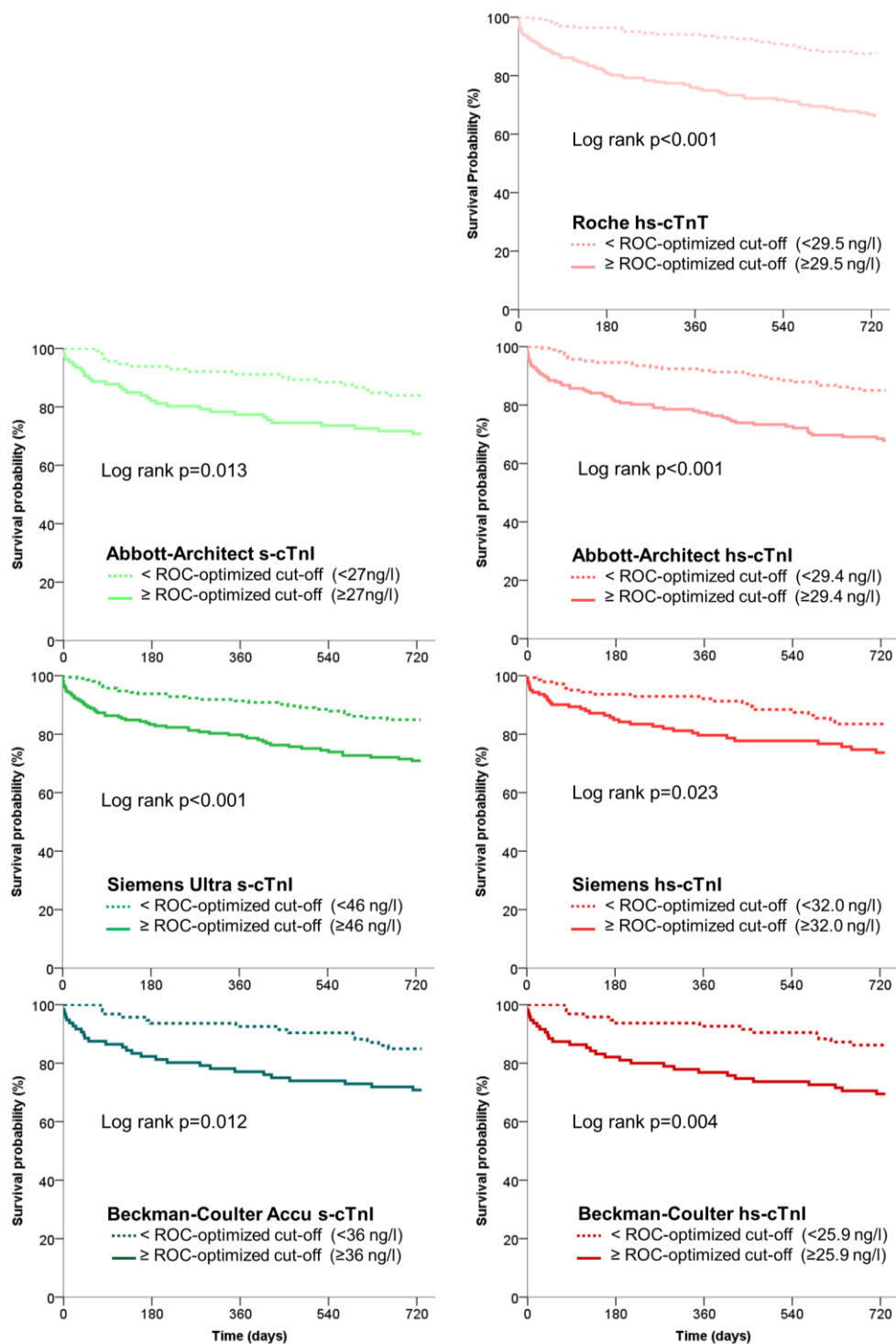
Correlations between renal function expressed by the glomerular filtration rate (GFR) and levels of cardiac troponin at presentation in patients without acute myocardial infarction.



**Supplemental
Figure 3**

Two-year survival curves based on presence of renal dysfunction.

Kaplan-Meier curves displaying the two-year survival rates for patients with normal renal function (survival probability 96%) and for patients with renal dysfunction (survival probability 79%).



**Supplemental
Figure 4**

Two-year survival in patients with renal dysfunction stratified according to ROC-optimized diagnostic cut-off levels.

Kaplan-Meier curves displaying the two-year survival rates based on receiver operating characteristic (ROC) – optimized cut-off levels of sensitive (green, s-cTn) and high-sensitivity (red, hs-cTn) cardiac troponin assays.

Supplemental References

1. Apple FS, Wu AH, Jaffe AS. European society of cardiology and american college of cardiology guidelines for redefinition of myocardial infarction: How to use existing assays clinically and for clinical trials. *Am Heart J.* 2002;144:981-986
2. Apple FS, Jesse RL, Newby LK, Wu AH, Christenson RH, National Academy of Clinical B, Damage ICfSoMoC. National academy of clinical biochemistry and ifcc committee for standardization of markers of cardiac damage laboratory medicine practice guidelines: Analytical issues for biochemical markers of acute coronary syndromes. *Circulation.* 2007;115:e352-355
3. Reichlin T, Irfan A, Twerenbold R, Reiter M, Hochholzer W, Burkhalter H, Bassetti S, Steuer S, Winkler K, Peter F, Meissner J, Haaf P, Potocki M, Drexler B, Osswald S, Mueller C. Utility of absolute and relative changes in cardiac troponin concentrations in the early diagnosis of acute myocardial infarction. *Circulation.* 2011;124:136-145
4. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, Katus HA, Newby LK, Ravkilde J, Chaitman B, Clemmensen PM, Dellborg M, Hod H, Porela P, Underwood R, Bax JJ, Beller GA, Bonow R, Van der Wall EE, Bassand JP, Wijns W, Ferguson TB, Steg PG, Uretsky BF, Williams DO, Armstrong PW, Antman EM, Fox KA, Hamm CW, Ohman EM, Simoons ML, Poole-Wilson PA, Gurfinkel EP, Lopez-Sendon JL, Pais P, Mendis S, Zhu JR, Wallentin LC, Fernandez-Aviles F, Fox KM, Parkhomenko AN, Priori SG, Tendera M, Voipio-Pulkki LM, Vahanian A, Camm AJ, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Widimsky P, Zamorano JL, Morais J, Brener S, Harrington R, Morrow D, Lim M, Martinez-Rios MA, Steinhubl S, Levine GN, Gibler WB, Goff D, Tubaro M,

- Dudek D, Al-Attar N. Universal definition of myocardial infarction. *Circulation*. 2007;116:2634-2653
5. Vasile VC, Saenger AK, Kroning JM, Jaffe AS. Biological and analytical variability of a novel high-sensitivity cardiac troponin t assay. *Clin Chem*. 2010;56:1086-1090
 6. Wu AH, Lu QA, Todd J, Moecks J, Wians F. Short- and long-term biological variation in cardiac troponin i measured with a high-sensitivity assay: Implications for clinical practice. *Clin Chem*. 2009;55:52-58
 7. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, Bickel C, Baldus S, Warnholtz A, Frohlich M, Sinning CR, Eleftheriadis MS, Wild PS, Schnabel RB, Lubos E, Jachmann N, Genth-Zotz S, Post F, Nicaud V, Tiret L, Lackner KJ, Munzel TF, Blankenberg S. Sensitive troponin i assay in early diagnosis of acute myocardial infarction. *N Engl J Med*. 2009;361:868-877
 8. Apple FS, Pearce LA, Smith SW, Kaczmarek JM, Murakami MM. Role of monitoring changes in sensitive cardiac troponin i assay results for early diagnosis of myocardial infarction and prediction of risk of adverse events. *Clin Chem*. 2009;55:930-937
 9. Hammarsten O, Fu ML, Sigurjonsdottir R, Petzold M, Said L, Landin-Wilhelmsen K, Widgren B, Larsson M, Johanson P. Troponin t percentiles from a random population sample, emergency room patients and patients with myocardial infarction. *Clin Chem*. 2012;58:628-637
 10. Melanson SE, Morrow DA, Jarolim P. Earlier detection of myocardial injury in a preliminary evaluation using a new troponin i assay with improved sensitivity. *Am J Clin Pathol*. 2007;128:282-286
 11. Apple FS, Smith SW, Pearce LA, Ler R, Murakami MM. Use of the centaur tni-ultra assay for detection of myocardial infarction and adverse events in patients

presenting with symptoms suggestive of acute coronary syndrome. *Clin Chem.* 2008;54:723-728

12. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, Biedert S, Schaub N, Buerge C, Potocki M, Noveanu M, Breidthardt T, Twerenbold R, Winkler K, Bingisser R, Mueller C. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med.* 2009;361:858-867
13. Stiegler H, Fischer Y, Vazquez-Jimenez JF, Graf J, Filzmaier K, Fausten B, Janssens U, Gressner AM, Kunz D. Lower cardiac troponin t and i results in heparin-plasma than in serum. *Clin Chem.* 2000;46:1338-1344
14. Apple FS. A new season for cardiac troponin assays: It's time to keep a scorecard. *Clin Chem.* 2009;55:1303-1306
15. Mingels A, Jacobs L, Michielsen E, Swaanenburg J, Wodzig W, van Dieijen-Visser M. Reference population and marathon runner sera assessed by highly sensitive cardiac troponin t and commercial cardiac troponin t and i assays. *Clin Chem.* 2009;55:101-108
16. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin t assay. *Clin Chem.* 2010;56:254-261
17. Apple FS, Collinson PO, Biomarkers ITFoCAoC. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clin Chem.* 2012;58:54-61
18. Panteghini M, Pagani F, Yeo KT, Apple FS, Christenson RH, Dati F, Mair J, Ravkilde J, Wu AH, Committee on Standardization of Markers of Cardiac Damage of the I. Evaluation of imprecision for cardiac troponin assays at low-range concentrations. *Clin Chem.* 2004;50:327-332

19. Kavsak PA, Hill SA, McQueen MJ, Devereaux PJ. Implications of adjustment of high-sensitivity cardiac troponin t assay. *Clin Chem*. 2013;59:574-576
20. Kavsak PA, MacRae AR, Yerna MJ, Jaffe AS. Analytic and clinical utility of a next-generation, highly sensitive cardiac troponin i assay for early detection of myocardial injury. *Clin Chem*. 2009;55:573-577
21. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics*. 1988;44:837-845
22. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (roc) curve. *Radiology*. 1982;143:29-36
23. Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950;3:32-35
24. Simel DL, Samsa GP, Matchar DB. Likelihood ratios with confidence: Sample size estimation for diagnostic test studies. *J Clin Epidemiol*. 1991;44:763-770

Optimal Cutoff Levels of More Sensitive Cardiac Troponin Assays for the Early Diagnosis of Myocardial Infarction in Patients With Renal Dysfunction

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